(54) Title: NON-STEROID ANDROGEN RECEPTOR ANTAGONISTS

(57) Abstract

Non-steroidal compounds of formulae (I) or (II), wherein the variables are as defined in the description, which are high affinity, high specificity ligand antagonists for the androgen receptor are disclosed. Also disclosed are methods for employing the disclosed compounds for modulating processes mediated by the androgen receptor and for treating patients requiring androgen receptor antagonist therapy.

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# DESCRIPTION

## NON-STEROID ANDROGEN RECEPTOR ANTAGONISTS

### Field of the Invention

This invention relates to intracellular receptors and ligands therefor. More specifically, this invention relates to compounds which are non-steroidal androgen

5   receptor antagonists, and methods for use of such compounds or ligands.

### Background of the Invention

A central problem in eukaryotic molecular biology continues to be the elucidation of molecules and mech-

10   anisms that mediate specific gene regulation in response to molecular inducers such as hormones. As part of the scientific attack on this problem, a great deal of work has been done in efforts to identify molecular inducers which are capable of mediating specific gene regulation.

15   Although much remains to be learned about the specifics of gene regulation, it is known that certain small molecule, non-peptide hormones and similarly acting vitamins and vitamin metabolites (collectively hereinafter called "hormones") modulate gene transcription by acting

20   in concert with intracellular components, including intracellular receptors and discrete DNA promoter enhancer sequences known as hormone response elements (HREs).

These hormones, acting through, and as "ligands" for, their intracellular receptors, directly regulate hormone-

25   responsive genes (and perhaps other important genes which are not directly hormone-responsive). Natural ligands for intracellular receptors are synthesized in the body or may be taken in as a component of food. It has also been shown that compounds other than the natural ligands can

30   act upon intracellular receptors to regulate hormone-responsive genes. For example, some natural product

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derivatives and synthetic compounds also function as ligands for these receptors.

Intracellular receptors form a class of structurally-related genetic regulators scientists have named "ligand
5   dependent transcription factors." Regulation of a gene by such factors requires both the intracellular receptor itself and a corresponding ligand which has the ability to selectively bind to the intracellular receptor in a way that affects gene activity. Until bound by a ligand, the
10  intracellular receptor is unable to exert an effect on the gene. Hormone or other ligand molecules in the fluid surrounding a cell pass through the outer cell membrane by passive diffusion. Once inside the cell, the ligand binds to specific intracellular receptor proteins, creating a
15  ligand/receptor complex. The binding of the ligand to its receptor induces a change in the shape of the intra-cellular receptor. This conformational change is believed to expose regions of the intracellular receptor that permit the intracellular receptor/ligand complex to bind
20  to a specific subset of genes present in the cell's DNA in the cell nucleus.

The blueprint to build specific proteins is encoded in the DNA sequence of each gene. This blueprint is copied in a process referred to as "transcription," to give rise
25  to the actual template for the production of specific proteins, messenger RNA or "mRNA". The MRNA then moves from the cell's nucleus into the cytoplasm and is trans-lated, which results in the production of proteins encoded in the MRNA. Accordingly, a reduction in the transcrip-
30  tion of MRNA reduces the production of the specific proteins.

Once the intracellular receptor/ligand complex binds to the specific site on the DNA, it alters the amount of the protein encoded by the gene that the cell is directed
35  to produce, by altering the amount of MRNA transcribed by that gene. A ligand which binds an intracellular receptor and mimics the effect of the natural ligand is referred to

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as an "agonist" ligand. A ligand that inhibits the effect of the hormone is called an "antagonist." Intracellular receptors are referred to as "ligand-dependent transcription factors" because their activity is dependent upon the

5   binding of their hormones or other ligands, which are necessary to drive the intracellular receptor into its active conformation.

The intracellular receptors form a large family of proteins that are closely related in structure. They are

10  important drug targets, and many drugs currently on the market are ligands for these intracellular receptors. Not surprisingly, the structural similarity of the intracellular receptors often results in cross-reactivity between a drug and one or more intracellular receptors

15  other than the desired target intracellular receptor. It is apparent, therefore, that there is a need to find alternative ligands (agonists and/or antagonists) which are readily available for therapeutic administration, have added specificity for particular intracellular receptors,

20  and have increased activity.

Ligands to the androgen receptor are known to play an important role in prostatic hyperplasia, including cancer of the prostate and benign prostatic hypertrophy, male pattern baldness, acne, idiopathic hirsutism, Stein-

25  Leventhal syndrome, mammary cancers and other health care problems.    Thus, antagonists to testosterone, the endogenous-hormone of the androgen receptor, are useful in treating chronic disorders such as those described above. In addition, the identification of compounds which inter-

30  act with the androgen receptor, and thereby affect transcription of genes which are responsive to testosterone, would be of significant value, e.g., for therapeutic applications such as treatment of hormonally-responsive benign and malignant disorders.

35  Further, the identification of compounds which have good specificity for the androgen receptor, but which have less cross-reactivity for other intracellular receptors,

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would be of significant value since interaction of a
ligand with other than the target intracellular receptors
is known to result in significant undesirable pharmaco-
logical side effects. Accordingly, antagonists to the
5    androgen receptor which do not display cross-reactivity
with other intracellular receptors (e.g., glucocorticoid
receptor and mineralocorticoid receptor) will exhibit an
improved therapeutic index.

A group of prenylated bromohydroquinones, called
10   collectively cymopols, has been isolated and identified by
several investigators using as a starting material the
green marine alga _Cymopolia_ _barbata_ (L.) Lamouroux
(Dasycladaceae). Among these, cymopol, $C_{16}H_{21}BrO_2$, is a
crystalline phenol which has a bromogeranyl-hydroquinone
15   or brominated monoterpene-quinol structure. As described
by Högberg et al., J.C.S. Perkin I, 1696-1701 (1976),
cymopol    [2-bromo-5-(3,7-dimethylocta-2,6-dienyl)
hydroquinone] and its monomethyl ether, $C_{17}H_{23}BrO_2$, have the
following structures:



Cymopol



20                         Cymopol monomethyl ether

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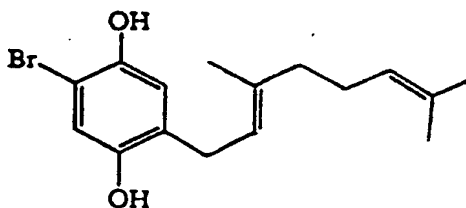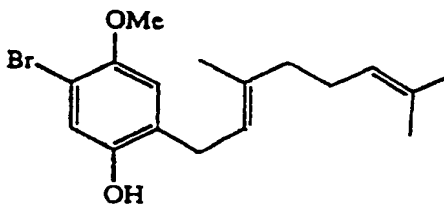
Cyclocymopol [1-bromo-3-(4-bromo-2,5-dihydroxybenzyl)-
2,2-dimethyl-4 methylene cyclohexane] and its monomethyl
ether have also been obtained from C. barbata. See
Högberg et al., supra. As described in McConnell et al.,
5    Phytochemistry, Vol. 21, No. 8, pp. 2139-41 (1982), C.
barbata contains a mixture of optically active diastereo-
mers of cyclocymopol, $C_{16}H_{20}Br_2O_2$, and cyclocymopol mono-
methyl ether, $C_{17}H_{22}Br_2O_2$, having the following structures:
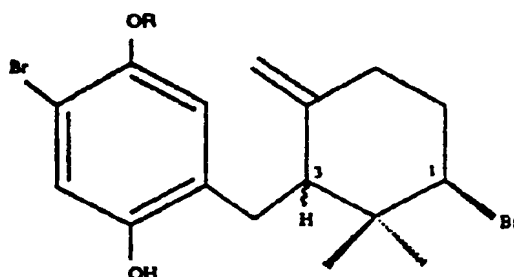


1a  (R=H): 2a  (R=Me): H  (C-3)-pseudo-equatorial
10       1b  (R=H): 2b  (R=Me): H  (C-3)-pseudo-axial
(The above assumes the equatorial conformation for bromine
at C-1).

Through silica gel chromatography of an ether-soluble
extract of C. barbata, McConnell et al. were able to
15   obtain a 1:1 mixture of α:β epimers of cyclocymopol.
McConnell et al. also obtained a 3:1 mixture of α:β
epimers of cyclocymopol monomethyl ether, which was
enriched to a 4:1 mixture of the 'α:β epimers through
purification techniques.

20       Wall et al., J. Nat. Prod., Vol. 52, No. 5, pp. 1092-
99 (1989), described additional diastereomeric cymopol
compounds (cymobarbatol and 4-isocymobarbatol) which were
determined to be highly active antimutagens. Wall et al.
reported obtaining pure cymobarbatol compounds, but were
25   unable to obtain stable cyclocymopol fractions.
Apparently, however, the forms of cyclocymopol and

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cyclocymopol monomethyl ether obtained by Högberg et al.,
supra, were pure forms of formulae 1b and 2b above.

The publications and references referred to above and
hereafter in this specification are expressly incorporated
5  herein by reference.


Summary of the Invention

The present invention is directed to compounds, compo-
sitions, and methods for modulating processes mediated by
the androgen receptor.  More particularly, the invention
10  relates to non-steroidal compounds which are high affin-
ity, high specificity ligands for the androgen receptor
(AR).  These compounds exhibit AR antagonist activity, and
modulate processes mediated by AR.  Accordingly, the
invention also relates to methods for modulating processes
15  mediated by AR employing the compounds disclosed.
Examples of compounds used in and forming part of the
invention include synthetic cyclocymopol analogs, and
semi-synthetic derivatives of natural cyclocymopols.
Pharmaceutical compositions containing the compounds dis-
20  closed are also within the scope of this invention.  Also
included are methods for identifying or purifying AR by
use of the compounds of this invention.


Definitions

In accordance with the present invention and as used
25  herein, the following terms are defined with the following
meanings, unless explicitly stated otherwise.

The term alkyl refers to straight-chain, branched-
chain, cyclic structures, and combinations thereof.

The term "aryl" refers to aromatic groups which have
30  at least one ring having a conjugated pi electron system
and includes carbocyclic aryl, heterocyclic aryl and
biaryl groups, all of which may be optionally substituted,
being preferably phenyl or phenyl substituted by one to
three substituents, such substituents being advantageously
35  lower alkyl, hydroxy, lower alkoxy, lower acyloxy,

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halogen, cyano, trihalomethyl, lower alcylamino, or lower
alkoxycarbonyl.

Carbocyclic aryl groups are groups wherein the ring
atoms on the aromatic ring are carbon atoms.  Carbocyclic
5   aryl groups include monocyclic carbocyclic aryl groups and
optionally substituted naphthyl groups.

Heterocyclic aryl groups are groups having from 1 to
3 heteroatoms as ring atoms in the aromatic ring with the
remainder of the ring atoms being carbon atoms.  Suitable
10  heteroatoms include oxygen, sulfur, and nitrogen, and
suitable heterocyclic aryl groups include furanyl,
thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolyl, pyri-
midyl, pyrazinyl, imidazolyl, and the like, all optionally
substituted.

15  The term "aralkyl" refers to an alkyl group substi-
tuted with an aryl group.  Suitable aralkyl groups include
benzyl and the like, and may be optionally substituted.

The term "lower" referred to herein in connection with
organic radicals or compounds respectively defines such
20  with up to and including 7, preferably up to and including
4 and advantageously one or two, carbon atoms.  Such
groups may be straight chain or branched.


Brief Description of the Drawings

The present invention may be better understood, and
25  its advantages appreciated by those skilled in the art by
referring to the accompanying drawings wherein:

Figure 1 presents activation profiles for analysis of
androgen receptor by increasing concentrations of dihydro-
testosterone (DHT) (•) and the antagonist dose response
30  profile of 2-Hydroxy-flutamide (+) at a constant concen-
tration of 5 x 10-9 M DHT;

Figure 2 presents antagonist activation profiles for
analysis of androgen receptor by derivative compound "A"
(•) and for derivative compound "B" (+); and

35  Figure 3 presents antagonist activation profiles for
analysis of androgen receptor by derivative compound "B"

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(•), derivative compound "C" (+), and derivative compound "D" (*).


Detailed Description of Embodiments of the Invention

    Cyclocymopols useful in this invention are defined as
5   those having the formulae:
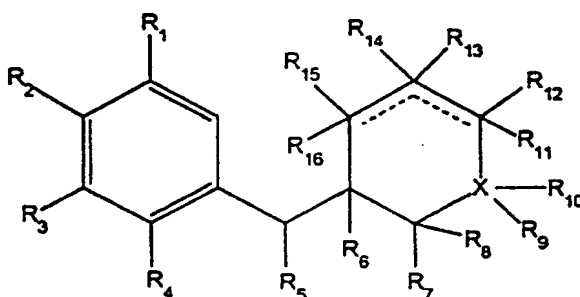


or
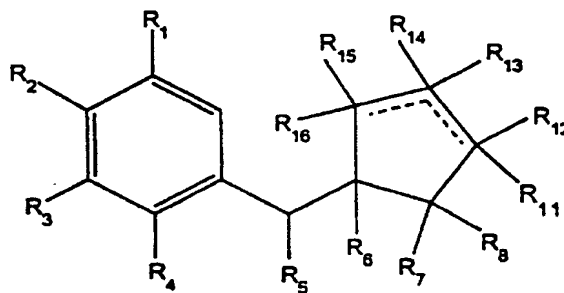


wherein:

    the dotted lines in the structure depict optional
double bonds;

10      X is carbon, oxygen, or nitrogen;

    $R_1$ is $R_{17}$, -$OR_{17}$, -$N(R_{17})(R_{17'})$, -$SR_{17}$, fluorine, chlorine,
bromine, or -$NO_2$;

    $R_{17}$, and ($R_{17'}$), each independently, are hydrogen,
saturated or unsaturated $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_5$-$C_7$

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aryl, or C$_7$ aralkyl, said alkyl groups being branched or straight-chain;

R$_2$ is -NO$_2$, -N(OH)R$_{17}$, fluorine, chlorine, bromine, iodine, R$_{17}$, -N(R$_{17}$)(R$_{17'}$), -SR$_{17}$, -S(O)-R$_{17}$, -S(O)$_2$-R$_{17}$, -CH$_2$OH, -C(O)CH, -C(O)CH$_3$, -C(O)-OCH$_3$, -C=CH$_2$, -C=CH-C(O)-OCH$_3$, or R$_{18}$;

R$_{18}$ and (R$_{18'}$), each independently, are hydrogen, saturated or unsaturated C$_1$-C$_6$ alkyl, C$_3$-C$_7$ cycloalkyl, C$_5$-C$_7$ aryl, or C$_7$ aralkyl, said alkyl groups being branched or straight-chain which optionally may contain hydroxyl, aldehyde, ketone, nitrile, or ester groups;

R$_3$ is R$_{17}$ or -OR$_{17}$;

R$_4$ is hydrogen, -OR$_{17}$, -OC(O)R$_{17}$, -OC(O)OR$_{17}$, -OC(O)N(R$_{17}$)(R$_{17'}$), -OS(O)$_2$R$_{17}$, or -OS(O)-R$_{17}$;

R$_5$ is hydrogen or OR$_{17}$;

R$_6$ is R$_{17}$;

R$_7$ and R$_8$, each independently, are R$_{18}$, or R$_7$ and R$_8$ together are a carbocyclic 3-8 member ring;

R$_9$ and R$_{10}$, each independently, are chlorine, bromine, or R$_{17}$, or R$_9$ and R$_{10}$, combined are =O, except when X=O, R$_9$ and R$_{10}$ are not present, and when X is N, then R$_{10}$ is not present, or R$_9$ and R$_{10}$ together are joined in a carbocyclic 3-8 member ring;

R$_{11}$ and R$_{12}$, each independently, are -OR$_{17}$, R$_{18}$, are =O, or are =CH$_2$, except when R$_{11}$ is attached to an sp$^2$ carbon atom in the ring, then R$_{12}$ is not present and R$_{11}$ is R$_{18}$,

or R$_{11}$ and R$_{13}$ together are joined in a carbocyclic 3-8 member ring or are -O- to form an epoxide;

R$_{13}$ and R$_{14}$, each independently, are -OR$_{17}$ or R$_{18}$, except when R$_{13}$ is attached to an sp$^2$ carbon atom in the ring, then R$_{14}$ is not present and R$_{13}$ is -OR$_{17}$ or R$_{18}$;

R$_{15}$ and R$_{16}$, each independently, are R$_{18}$ or OR$_{17}$, or R$_{15}$ and R$_{16}$ together are -CH$_2$-O- forming an epoxide, or R$_{15}$ and R$_{16}$ combined are =O or =C(R$_{18}$)(R$_{18'}$), except when R$_{15}$ is hydroxyl, then R$_{16}$ is not hydroxyl, and when R$_{15}$ is attached to an sp$^2$ carbon atom in the ring, then R$_{16}$ is not present,

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or $R_{15}$ and $R_{16}$ together are joined in a carbocyclic 3-8 member ring.

Representative compounds and derivatives according to the present invention include the following:

5      1-Methylidene-6-(3'-nitrophenyl)methyl-5,5-dimethyl-cyclohex-2-ene;

(1S,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethylcyclohexane;

1-Methylidene-6-(2'-hydroxyphenyl)methyl-5,5-dimethyl-
10    cyclohex-2-ene;

1-Methylidene-2-(2'-hydroxyphenyl)methyl-5,5-dimethyl-cyclohexane;

(4S,6S)-1-Methylidene-4-bromo-5-(2'-acetoxy-4'-bromo-5'-methyoxyphenyl) methyl-5,5-dimethylcyclohex-2-ene;

15    1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl) methyl-5,5-dimethylcyclohex-2-ene;

2-(4'-Nitrophenyl)methylcyclohexan-1-one;

8-(2'-Acetoxy-4'-bromo-5'-methoxyphenyl)methyl-5,7,7-trimethylspiro[2.5]oct-4-ene;

20    trans-2-(4'-Nitrophenyl)methylcyclohexan-1-ol;

(1S,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-1,4,4-trimethylcyclohexane;

1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl) methyl-3,3-dimethylcyclopentane;

25    (5R,6S)-1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl)methyl-5-methylcyclohex-2-ene;

1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl) methyl-3,3-dimethylcyclohexane;

(2R)-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxy-
30    phenyl)methyl-3,3-dimethylcyclohexane;

(5R,6S)-1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl)methyl-3,5-dimethylcyclohex-2-ene;

(1R,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-1,4,4-trimethylcyclohexane;

35    trans-1-Methyl-2-(2'-hydroxy-4'-bromo-5'-methoxy-phenyl)methylcyclohexan-1-ol;

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(1R,3R)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethylcyclohexane;

cis-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-3,3,5-trimethylcyclohexane;

5      1-Methylidene-6-(3'-methyl-4'-nitrophenyl)methyl-5,5-dimethylcyclohex-2-ene;

1-Methylidene-6-(4'-nitro-3'-methylphenyl)methyl-3,5,5-trimethylcyclohex-2-ene;

2-(4'-Nitrophenyl)methyl-3,3-dimethylcyclohexan-1-one;

10      1-Methylidene-6-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-5,5-dimethylcyclohex-2-ene;

(2S)-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-3,3-dimethylcyclohexane; and

2-(2'-Hydroxy-4'-bromo-5'-methoxyphenyl) methylcyclo-
15   hex-1-one.

Compounds comprising the class of synthetic cyclo-cymopol analogs and derivatives disclosed herein can be obtained by routine chemical synthesis by those skilled in the art, e.g., by modification of the cyclocymopol
20   compounds disclosed or by a total synthesis approach.

The invention will be further illustrated by reference to the following non-limiting Examples. All parts and percentages are expressed as parts by weight unless otherwise indicated.

25   Example 1

Synthetic and semisynthetic cyclocymopol analogs have been prepared which display antagonist activity for the intracellular receptor for androgen. Representative analogs of the present invention are prepared according to
30   the following illustrative synthetic schemes and illustrative Examples.

Synthesis of Aromatic Subunit
2-Acetoxy-5-methoxybenzaldehyde (1):

To a flame-dried 50 mL round-bottomed flask containing
35   10.00 g (65.7 mmol) 2-hydroxy-5-methoxybenzaldehyde in 10

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mL dry pyridine at 0°C under nitrogen atmosphere was added
7 mL acetic anhydride. The reaction mixture was then
allowed to warm to room temperature and continually
stirred until thin-layer chromatography (TLC) analysis
5  indicated complete consumption of starting material (50
min). Ethyl acetate (150 mL) was added, and the mixture
was then transferred to a separatory funnel and success-
ively washed with 1N HCl (3 x 50 mL), saturated aqueous
NaHCO₃, (1 x 50 mL), and brine (1 x 50 mL), dried over
10  Na₂SO₄, and concentrated under reduced pressure to give
12.41 g (97%) of the acetylated phenol as a white solid.
The product thus obtained was homogenous by TLC (Rf 0.41,
2:1 hexane/ethyl acetate), and was carried on to the next
step without further purification.

15  <u>2-Acetoxy-4-bromo-5-methoxybenzaldehyde (2)</u>:

To a 500 mL round-bottomed flask containing a solution
of 20.0 g (168.1 mmol, 3.26 equiv) potassium bromide and
3.21 mL (10.0 g, 62.6 mmol, 1.21 equiv) bromine in 200 mL
water at room temperature was added 10.00 g (51.5 mmol,
20  1.0 equiv) 2-acetoxy-5-methoxybenzaldehyde (1) as a finely
divided white powder, portionwise over a period of 35 min.
After 18 h stirring at room temperature, the reaction
mixture was filtered under vacuum using a Büchner funnel
to give 10.59 g (89%) of the aryl bromide as a pale yellow
25  solid (Rf 0.45, 2:1 hexanes/ethyl acetate). The product
thus obtained was of greater than 98% purity by ¹H NMR, and
homogenous by TLC, and was carried on to the next step
without further purification. A portion of the crude
product was recrystallized from 5:1 ether/hexanes to give
30  white needles. ¹H NMR (400 MHz, CDCl₃) δ 2.37 (s, 3H,
COCH₃), 3.93 (s,3H, OCH₃), 7.36 and 7.46 (2s, 2 x 1H, Ar-
H), 10.08 ppm (s, 1H, CHO).

<u>2-Hydroxy-4-bromo-5-methoxybenzaldehyde (3)</u>:

To a 200 mL round-bottomed flask containing 6.90 g
35  (25.3 mmol) 2 acetoxy-4-bromo-5-methoxybenzaldehyde (2) in

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100 mL of 1% aqueous methanol at room temperature was added 5 g K$_2$CO$_3$, and the mixture was allowed to stir at room temperature for 1 h, at which time TLC analysis indicated complete consumption of starting material and the

5    presence of a slightly more polar compound as the only detectable product. The reaction mixture was then neutralized to pH 5 with the addition of 1 N HCl, and the solvent was subsequently removed under diminished pressure. The residue was then dissolved in ethyl acetate (200 mL),

10   washed successively with 1 N HCl (1 x 50 mL), saturated aqueous NaHCO$_3$ (1 x 50 mL), and brine (1 x 50 mL), dried over Na$_2$SO$_4$, and concentrated under diminished pressure to give 4.97 g (85%) of the bromophenol as a brownish-red oily solid.  A portion of this crude material was

15   recrystallized from 2:1 hexanes/ethyl acetate to give white needles. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.89 (s, 3H, OCH$_3$), 6.97 and 7.27 (2s, 2 x 1H, Ar-H), 9.83 (s, 1H, OH), 10.71 ppm (s, 1H, CHO). The remainder of the material was carried on to the next step without further purification.

20   <u>2-(*tert*-Butyl)dimethylsilyloxy-4-bromo-5-methoxybenzaldehyde (4)</u>:

     To a flame-dried 100 mL round-bottomed flask containing 2.76 g (11.95 mmol) 2-hydroxy-4-bromo-5-methoxybenzaldehyde (3) in 50 mL anhydrous dichloromethane under

25   nitrogen atmosphere at room temperature was added 2.03 g (29.88 mmol, 2.50 equiv) imidazole, 2.25 g (14.94 mmol, 1.25 equiv) (*tert*-butyl)-dimethylchlorosilane, and 4-N,N'-dimethyl propyleneurea (DMAP) (100 mg, catalytic). The mixture was allowed to stir at room temperature for 75

30   min, at which time TLC analysis indicated complete consumption of starting material, and the formation of a less polar product (Rf 0.75, 2:1 hexanes/ethyl acetate). The reaction mixture was then poured into a separatory funnel containing 50 mL dichloromethane and 50 mL satur-

35   ated aqueous NH$_4$Cl, the layers were separated, and the organic phase was washed with 50 mL brine, dried over

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Na$_2$SO$_4$, and concentrated under diminished pressure to give
4.13 g (quantitative) of the silylated bromophenol as an
off-white solid, a portion of which was recrystallized
from 3:1 hexanes/ether to give an amorphous white solid.

5 $^1$H NMR (400 MHz, CDCl$_3$) δ 0.27 [s, 6H, Si(CH$_3$)$_2$], 1.02 [s,
9H, SiC(CH$_3$)$_3$], 3.89 (s, 3H, OCH$_3$), 7.14 (s, 1H, 6-H), 7.28
(s, 1H, 3-H), 10.35 ppm (s, 1H, CHO); $^{13}$C NMR (100.61 MHz,
CDCl$_3$) δ -4.4, 18.3, 25.7, 56.6, 108.9, 120.1, 125.6,
126.5, 151.0, 152.9, 189.1 ppm.

10 2-(tert-Butyl)dimethylsilyloxy-4-bromo-5-methoxybenzyl
alcohol (5):

To a flame-dried 200 mL round-bottomed flask contain-
ing 4.10 g (13.14 mmol) 2-(tert-butyl)dimethylsilyloxy-4-
bromo-5-methoxybenzaldehyde (4) in 100 mL anhydrous

15 methanol at 0°C was added 0.50 g (13.15 mmol, 1.0 mol
equiv) NaBH$_4$ over a period of 3 min. After 20 min at 0°C,
TLC analysis indicated complete consumption of starting
material, and the formation of a more polar product (Rf
0.42, 2:1 hexanes/ethyl acetate). Water (75 mL) was

20 added, and the methanol was removed by rotary evaporation.
The resultant aqueous residue was extracted with ethyl
acetate (2 x 100 mL), and the combined organic layers were
dried over Na$_2$SO$_4$, and concentrated under diminished
pressure. Purification by flash column chromatography

25 (silica gel, hexanes/ethyl acetate, 5:1) afforded 4.10 g
(98%) of the benzylic alcohol as a white solid. $^1$H NMR
(400 MHz, CDCl$_3$) δ 0.23 [s, 6H, Si(CH$_3$)$_2$], 1.00 [s, 9H,
SiC(CH$_3$)$_3$], 3.86 (s, 3H, OCH$_3$), 4.61 (s, 2H, CH$_2$OH), 6.92
(s, 1H, 6-H), 6.97 ppm (s, 1H, 3-H).

30 2-(tert-Butyl)dimethylsilyloxy-4-bromo-5-methoxybenzyl
bromide (6):

To a flame-dried 100 mL round-bottomed flask contain-
ing triphenylphosphine (1.27 g, 4.84 mmol, 1.05 equiv) in
25 mL anhydrous dimethylformamide (DMF) at 0°C under

35 nitrogen atmosphere was added bromine (0.24 mL, 4.84 mL,

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1.05 equiv, plus enough extra to cause a persistent red-
dish tint to the solution, 1 drop) through an additional
funnel. To this reaction mixture was added 2-(*tert*-butyl)
dimethylsilyloxy-4-bromo-5-methoxybenzyl    alcohol    (5)
through the addition funnel at a steady rate over 30 min,
as a solution in 10 mL DMF. The reaction mixture was
allowed to stir at 0°C for 60 min, at which time TLC
analysis  indicated  complete  consumption  of  starting
material, and the formation of a less polar product (Rf
0.81,  2:1  hexanes/ethyl  acetate).  Hexane  (100 mL)  was
then added, and the contents of the flask were transferred
to  a  separatory  funnel  containing  50  mL  of  saturated
aqueous $NH_4Cl$, rinsing with an additional 50 mL hexane and
10 mL water. The layers were separated, and the organic
phase was washed with 20 mL 10% $Na_2S_2O_3$, dried over $Na_2SO_4$,
and concentrated under diminished pressure. Purification
by  trituration  at  0°C  (2 x 30 mL ea.  hexanes)  to  remove
residual  triphenylphosphine  oxide,  followed  by  flash
column chromatography (silica gel, hexanes/ethyl acetate,
gradient  elution)  afforded  1.51  g  (80%)  of  the  benzylic
bromide as a colorless, viscous oil, which solidified upon
standing. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.27 [s, 6H, $Si(CH_3)_2$],
1.04 [s, 9H, $SiC(CH_3)_3$], 3.84 (s, 3H, $OCH_3$), 4.46 (s, 2H
$CH_2Br$), 6.87 and 7.01 ppm (2s, 2 x 1H, Ar-H).

25  2-(*tert*-Butyl)dimethylsilyloxybenzaldehyde (7):

This compound was prepared from salicylaldehyde (3.00
g, 24.1 mmol) in the manner previously described for the
synthesis of silyl ether (4), affording 4.23 g (74%) of
the silylated phenol as a colorless oil. $^1H$ NMR (400 MHz,
$CDCl_3$ $\delta$ 0.28 [s, 6H, $Si(CH_3)_2$], 1.03 [s, 9H, $SiC(CH_3)_3$],
6.88 (d, 1H, J = 8.5 Hz, Ar-H), 7.03 (dd, 1H, J = 7.4 Hz,
Ar-H), 7.46 (ddd, 1H, J = 8.6, 7.4, 2.0 Hz, Ar-H), 7.81
(dd, 1H, J = 7.7, 1.9 Hz, Ar-H), 10.47 ppm (s, 1H, CHO).

16

## 2-(tert-Butyl)dimethylsilyloxybenzyl alcohol (8):

This compound was prepared from 2-(*tert*-butyl) dimethylsilyloxybenzaldehyde (7) (4.23 g, 17.9 mmol) in the manner previously described for the synthesis of
5    benzyl alcohol 5, affording 2.81 g (66%) of the silyl-oxybenzyl alcohol as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.26 [s, 6H, Si(CH$_3$)$_2$], 1.02 [s, 9H, SiC(CH$_3$)$_3$], 4.68 (d, 2H, J = 6.3 Hz, CH$_2$OH), 6.81 (d, 1H, J = 6.3 Hz, Ar-H), 6.95 (dd, 1H, J = 7.1, 7.1 Hz, Ar-H), 7.17 (ddd,
10   1H, J = 9.5, 7.8, 1.7 Hz, Ar-H), 7.30 ppm (dd, 1H, J = 5.8, 1.6 Hz, Ar-H).

## 2-(tert-Butyl)dimethylsilyloxybenzyl bromide (9):

This compound was prepared from 2-(*tert*-butyl) dimethylsilyloxybenzyl alcohol (8) (2.81 g, 11.8 mmol) in
15   the manner previously described for the synthesis of benzyl bromide 6, affording 1.14 g (32%) of the silyl-oxybenzyl bromide as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.30 [s, 6H, Si(CH$_3$)$_2$], 1.07 [s, 9H, SiC(CH$_3$)$_3$], 4.54 (s, 2H, CH$_2$Br), 6.83 (d, 1H, J = 6.2 Hz, Ar-H), 6.93
20   (dd, 1H, J = 7.1, 7.1 Hz, Ar-H), 7.19 (ddd, 1H, J = 9.4, 7.9, 1.6 Hz, Ar-H), 7.34 ppm (dd, 1 H, J = 5.8, 1.6 Hz, Ar-H).
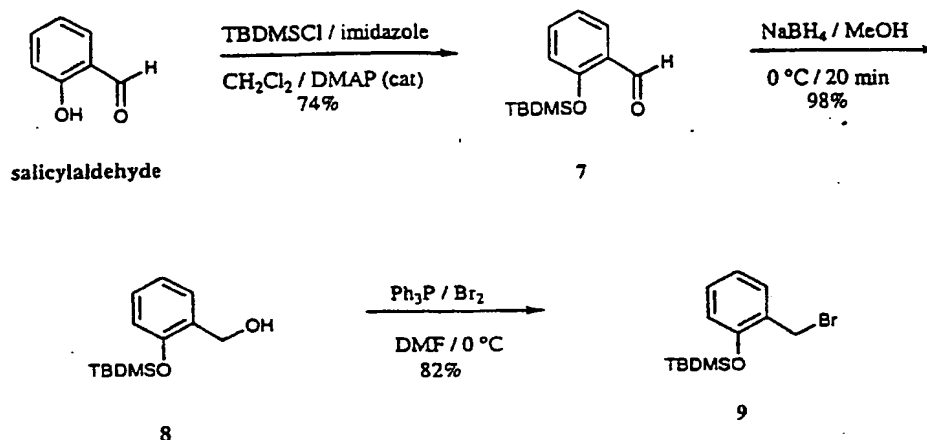
17

18



salicylaldehyde

7

8

9
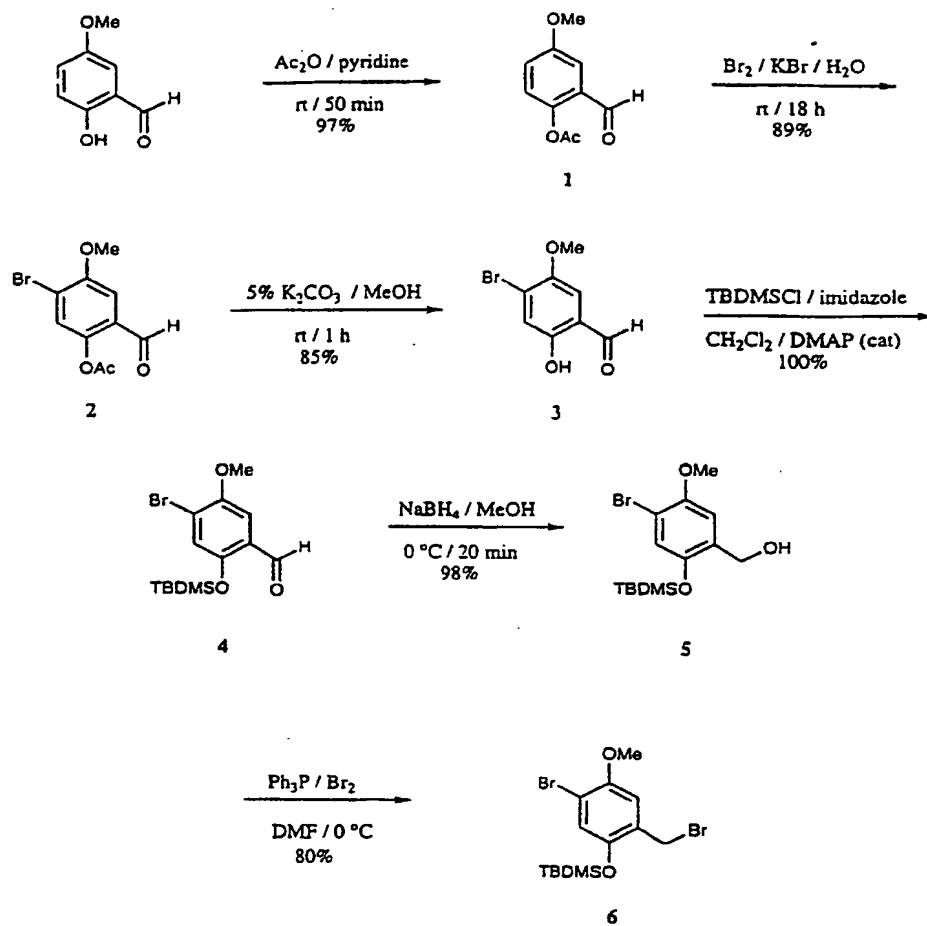
Example 2

Synthesis of Aliphatic Subunits

3-Ethoxy-5,5-dimethylcyclohex-2-en-1-one (10):

To a flame-dried 1 L round-bottomed flask containing
5   15.0 g (107 mmol) 5,5-dimethylcyclohexane-1,3-dione and
120 mL absolute ethanol in 300 mL anhydrous benzene under
nitrogen atmosphere was added 750 mg p-toluenesulphonic
acid monohydrate (catalytic). The flask was fitted with
a Dean Stark trap for removal of water, and a reflux
10  condenser, and the mixture was heated to reflux for 9 h.
Upon cooling to room temperature, the solvent was removed
by rotary evaporation, and the residue was dissolved in
300 mL ethyl acetate. The organic solution was then
washed successively with 10% aqueous NAOH (2 x 100 mL),
15  water (1 x 100 mL), and brine (1 x 100 mL), dried over
$Na_2SO_4$, and concentrated under diminished pressure to give
16.5 g (92%) of the keto-enol ether as a pale yellow oil
(Rf 0.24, 2:1 hexanes/ethyl acetate) of greater than 98%
purity by $^1H$ NMR. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.08 (s, 6H,
20  geminal-$CH_3$'s), 1.38 (dd, 3H, $OCH_2CH_3$), 2.21 and 2.28 (2s,
2 x 2H, 6-H, 4-H), 3.90 (q, 2H, $OCH_2CH_3$), 5.32 ppm (s, 1H,
2-H).

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## 5,5-Dimethylcyclohex-2-en-1-one (11):

To a flame-dried 100 mL round-bottomed flask contain-
ing lithium aluminum hydride (0.95 g, 24.4 mmol, 0.5 mol
equiv) in 35 mL anhydrous ether under nitrogen atmosphere
5  at 0°C was added 8.20 g (48.7 mmol) 3-ethoxy-5,5-
dimethylcyclohex-2-en-1-one (10) portionwise through a
syringe as a solution in 10 mL anhydrous ether. The
reaction mixture was allowed to warm to room temperature,
and after 4h, TLC analysis indicated complete consumption
10  of starting material. The reaction mixture was then
cooled to 0°C before the cautious addition of 50 mL water,
and the contents of the flask were then poured into a 500
mL Erlenmeyer flask containing 150 mL ice-cold 10% $H_2SO_4$.
The mixture was then extracted with ether (2 x 200 mL),
15  and the combined organics were washed successively with
water (100 mL), and saturated aqueous $NaHCO_3$ (100 mL),
dried over $Na_2SO_4$, and concentrated under diminished
pressure to give 6.05 g (quantitative) of the dimethyl-
enone (Rf 0.55, 2:1 hexane/ethyl acetate). $^1H$ NMR (400
20  MHz, $CDCl_3$) δ 1.05 (s, 6H, geminal-$CH_3$'s), 2.23 (dd, 2H, 4-
H), 2.28 (s, 2H, 6-H), 6.03 (ddd, 1H, 2-H), 6.87 ppm (ddd,
1H, 3-H).

20
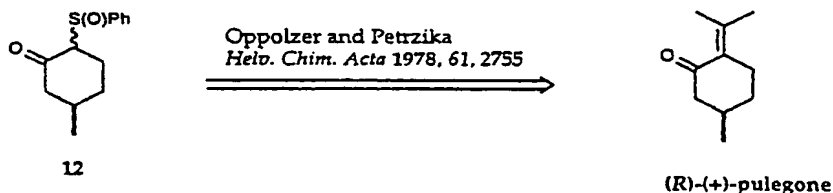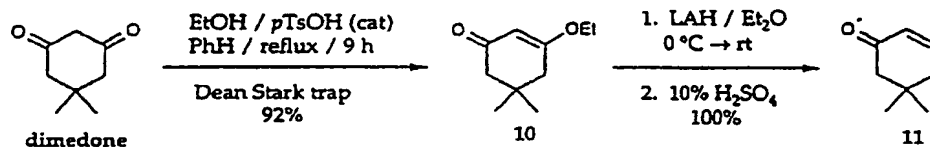
Synthesis of Analogs

Example 3

6-[2'-(tert-Butyl)dimethylsilyloxy-4'-bromo-5'-methoxy-
phenyl]methyl-5,5-dimethylcyclohex-2-en-1-one (13):

5        To a flame-dried 50 mL round-bottomed flask containing
diisopropylamine (0.188 mL, 1.34 mmol, 1.1 equiv) in 10 mL
anhydrous tetrahydrofuran (THF) at -78°C under nitrogen
atmosphere was added n-butyllithium (0.58 mL of a 2.2 M
solution in hexanes, 1.28 mmol, 1.05 equiv). After 20 min

10   at -78°C, 5,5-dimethylcyclohex-2-en-one (11) (0.151 g,
1.22 mmol) was added as a solution in 1 mL of THF, and the
reaction mixture was allowed to stir at that temperature
for 15 min, at which time the cooling bath was removed.
When the temperature of the reaction mixture (monitored

15   using a thermocouple probe) reached -5°C, 2-(tert-butyl)
dimethylsilyloxy-4-bromo-5-methoxybenzyl bromide (6) (1.00
g, 2.44 mmol, 2.0 equiv) was added all at once as a solu-
tion in 2 mL THF. The reaction mixture was then allowed
to warm to room temperature, and after 3 h, TLC analysis

20   indicated complete consumption of the enone starting
material, and the formation of a product of intermediate
polarity with respect to the two starting components (Rf
0.59, 2:1 hexanes/ethyl acetate), and the reaction was
quenched by the addition of 5 mL saturated aqueous $NH_4Cl$.

25   The contents of the flask were transferred to a separatory
funnel, and extracted with 60 mL ethyl acetate, and the
resultant organic phase was washed with 30 mL brine, dried
over $Na_2SO_4$, and concentrated under diminished pressure.
Purification by flash column chromatography (silica gel,

30   hexanes/ethyl acetate gradient elution) afforded 0.459 g
(83%) of the benzylated enone as a colorless, viscous oil,
which solidified on standing. $^1$H NMR (400 MHz, $CDCl_3$) δ
0.21 and 0.23 [2s, 2 x 3H, Si($CH_3$)$_2$], 1.00 [s, 9H,
SiC($CH_3$)$_3$], 1.02 and 1.03 (2s, 2 x 3H, geminal-$CH_3$'s), 2.25

35   an 2.32 (ddd of ABq, 2H, 4-H), 2.51 (dd, 1H, 6-H), 2.78
and 2.88 (d of ABq, 2H, benzylic-$CH_2$), 3.80 (s, 3H, O$CH_3$),

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5.96 (ddd, 1H, 2-H), 6.68 (s, 1H, 6'-H), 6.77 (ddd, 1H, 3-H), 6.94 ppm (s, 1H, 3'-H).


2-[2'-(tert-Butyl)dimethylsilyloxy-4'-bromo-5'-methoxyphenyl]methyl-3,3-dimethyl-cyclohexanone (14):

5      To a flame-dried round-bottomed flask containing 6-[2'-(tert-butyl)    dimethylsilyloxy-4'-bromo-5'-methoxy-phenyl]methyl-5,5-dimethylcyclohex-2-en-1-one (13) (0.154 g, 0.454 mmol) in 22 mL ethyl acetate (which had been pre-dried over $K_2CO_3$) at room temperature was added 20 mg 5%
10   palladium on carbon, and after flushing/evacuating the vessel 3 times with nitrogen, a hydrogen atmosphere was introduced and maintained by use of a balloon. After 24 h, the flask was again flushed several times with nitro-gen, and the contents of the flask were filtered, rinsing
15   with an additional 100 mL ethyl acetate. Rotary evapora-tion of the solvent afforded 0.156 g (quantitative) of the saturated benzylic ketone as a colorless, viscous oil (Rf 0.67, 2:1 hexanes/ethyl acetate). $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.22 and 0.25 [2s, 2 x 3H, Si(CH_3)_2], 0.87 and 1.12 (2s,
20   2 x 3H, geminal-CH_3's), 1.01 [s, 9H, SiC(CH_3)_3], 3.71 (s, 3H, OCH_3), 6.79 (s, 1H, 6'-H), 6.91 ppm (s, 1H, 3'-H).


1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl) methyl-3,3-dimethylcyclohexane (16):

     To a flame-dried 50 mL round-bottomed flask containing
25   2-[2'-(tert-butyl) dimethylsilyloxy-4'-bromo-5'-methoxy-phenyl]methyl-3,3-dimethylcyclohexanone (14) (0.130 g, 0.28 mmol) in 5 mL anhydrous THF at -78°C under nitrogen atmosphere was added (trimethyl)silylmethyllithium (0.420 mL of a 1.0 M solution in pentane, 0.42 mmol, 1.50 equiv).
30   An immediate change from colorless to a yellow reaction solution was observed, and TLC analysis at that time indicated complete consumption of starting material, and the formation of a less polar product (Rf 0.79, 2:1 hexanes/ethyl acetate), and the reaction was subsequently
35   quenched with 4 mL saturated aqueous NH_4Cl. Ethyl acetate

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(30 mL) extraction of the reaction mixture, drying over Na$_2$SO$_4$, and concentration under diminished pressure gave 0.152 g (quantitative) of a crude product (15), which appeared to be a single diastereomer of the ketone addi-
5   tion product by $^1$H NMR analysis. A portion of this crude intermediate (0.015 g, 0.028 mmol) was placed in a 10 mL Nalgene vial containing 2 mL THF, 0.2 mL of a premade HF pyridine complex was added, and the mixture was allowed to stir at room temperature for 32 h, at which time TLC
10  analysis indicated complete consumption of starting material, and formation of a more polar product, having passed through a most polar intermediate (confirmed as the desilylated phenol by $^1$H NMR). The contents of the reaction vessel were transferred to a separatory funnel
15  containing 20 mL ethyl acetate and 10 mL 1.0 M NaHSO$_4$. The layers were separated, and the resultant organic phase was washed with 10 mL brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate,
20  gradient elution) afforded 8.7 mg (92%) of the phenolic olefin as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.97 and 1.00 (2s, 2 x 3H, geminal-CH$_3$'s), 2.65 and 2.80 (d of ABq, $J_{AB}$ = 14.1 Hz, $J_A$ = 10.9 Hz, $J_B$ = 3.5 Hz, 2H, benzylic-CH$_2$), 3.80 (s, 3H, OCH$_3$), 4.36 (d, 1H, J = 1.0 Hz) and 4.64
25  (s, 1H) [methylidene-CH$_2$], 6.59 (s, 1H, 6'-H), 6.94 ppm (s, 1H, 3'-H); $^{13}$C NMR (100.61 MHz, CDCl$_3$) $\delta$ 23.5, 26.7, 28.1, 28.4, 32.4, 35.2, 36.1, 54.3, 57.0, 108.3, 110.3, 115.0, 120.1, 128.8, 148.0, 148.5, 150.0 ppm. [Compound 16 is hereinafter also referred to as COMPOUND "M" or 120019]

30  Examples 4-5
1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl)
methyl-5,5-dimethylcyclo-hex-2-ene (17):
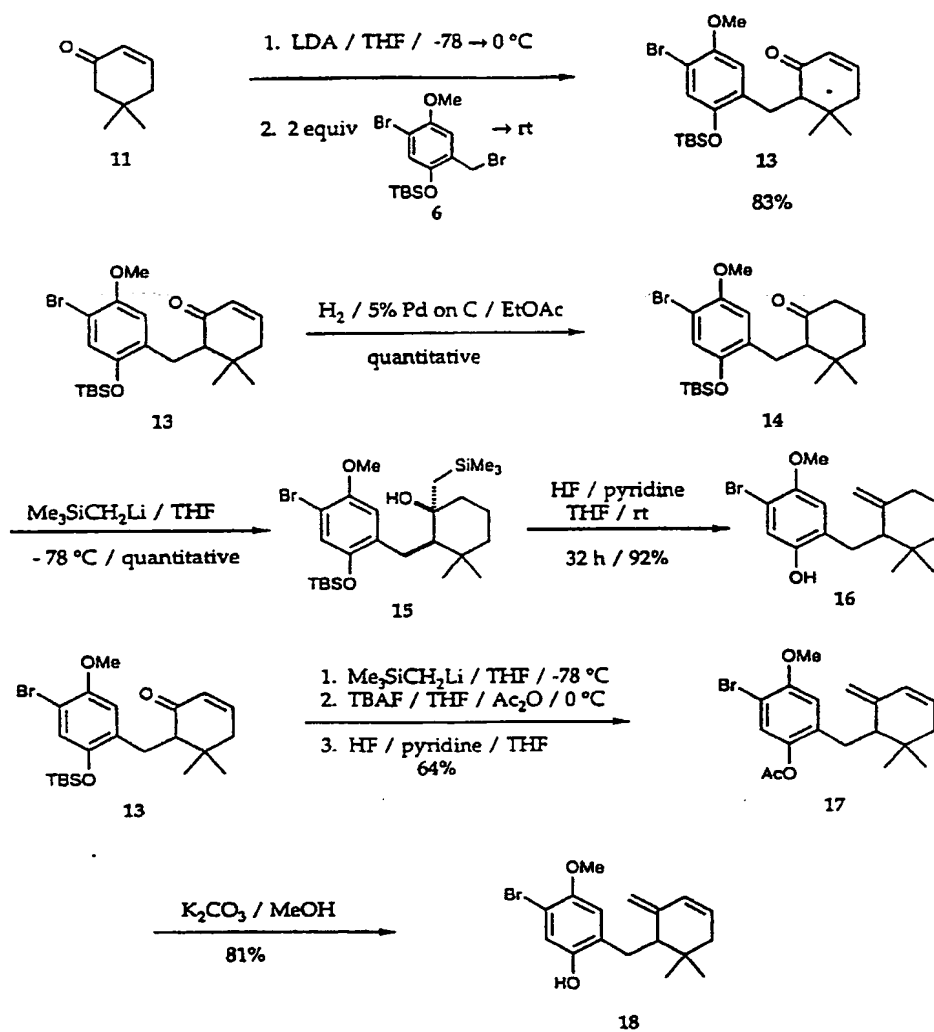    This compound was prepared from 6-[2'-(tert-butyl) dimethylsilyloxy-4'-bromo-5'-methoxyphenyl]methyl-5,5-
35  dimethylcyclohex-2-en-1-one (13) (0.075 g, 0.166 mmol) in the manner previously described for olefin 16, with the

23

following procedural changes necessitated by the incom-
patibility of structural features particular to this
substrate and the typical synthetic methodology.  Upon
formation of the initial (trimethyl)silylmethyllithium
5    addition adduct to enone 13, the phenolic protecting group
was exchanged prior to effecting elimination, using the
following protocol adhered to for all cyclocymopol analogs
incorporating the methylidene olefin into a 1,3-diene
moiety.  The crude addition product (0.090 g, 0.166 mmol)
10   was dissolved in 5 mL anhydrous THF containing 0.20 mL
acetic anhydride (large excess), and cooled to 0°C under
nitrogen atmosphere.   Tetra-(n-butyl)ammonium fluoride
(0.20 mL of a 1.0 M solution in THF, 0.20 mmol, 1.20
equiv) was added, and the mixture was allowed to warm to
15   room temperature.  The contents of the flask were then
poured into a separatory funnel containing 30 mL ethyl
acetate and 10 mL 1.0 M NaHSO$_4$, the layers were separated,
and the organic phase was washed with 10 mL brine, dried
over Na$_2$SO$_4$, and concentrated under diminished pressure.
20   The crude material thus obtained was immediately carried
on to the next step by transferring to a 10 mL Nalgene
vial containing 2-3 mL THF, and 0.3 mL premade HF/pyridine
complex was added.   After stirring overnight at room
temperature, the reaction mixture was worked up in the
25   usual manner, and purification by flash column chromato-
graphy (silica gel, hexanes/ethyl acetate, gradient
elution) afforded 38.3 mg (64%) of the desired acetoxy-
diene as a colorless, oily solid.  $^1$H NMR (400 MHz, CDCl$_3$)
δ 0.73 and 1.11 (2s, 2 x 3H, geminal-CH$_3$'s), 2.27 (s, 3H,
30   acetate-CH$_3$), 3.83 (s, 3H, OCH$_3$), 4.13 and 4.68 (2s, 2 x
1H, methylidene-CH$_2$), 5.70 and 6.04 (2dd, 2 x 1H, 2-H, 3-
H), 6.52 (s, 1H, 6'-H), 7.19 ppm (s, 1H, 3'-H).  [Compound
17 is hereinafter also referred to as COMPOUND "F" or
102032]

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<u>1-Methylidene-6-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)</u>
<u>methyl-5,5-dimethylcyclo-hex-2-ene (18):</u>

   In a 10 mL test tube was combined 1-methylidene-6-(2'-
acetoxy-4'-bromo-5'-methoxyphenyl)methyl-5,5-dimethyl-
5  cyclohexene (17) (10.0 mg, 0.026 mmol) and 2.0 mL of 5%
methanolic $K_2CO_3$. After 10 min at room temperature, the
methanol was removed by rotary evaporation, and the
resultant residue was dissolved in 20 mL ethyl acetate.
The organic solution was then washed with saturated
10  aqueous $NH_4Cl$, dried over $Na_2SO_4$, and concentrated under
diminished pressure. Purification by flash column chroma-
tography (silica gel deactivated with triethylamine,
hexanes/ethyl acetate, gradient elution) afforded 7.1 mg
(81%) of the phenolic diene as a colorless, oily solid.
15  $^1H$ NMR (400 MHz, $CDCl_3$) $\delta 0.73$ and 1.16 (2s, 2 x 3H,
geminal-$CH_3$'s), 3.82 (s, 3H, $OCH_3$), 4.23 and 4.72 (2s, 2 x
1H, methylidene-$CH_2$), 5.78 and 6.08 (2dd, 2 x 1H, 2-H, 3-
H), 6.51 (s, 1H, 6'-H), 6.99 ppm (s, 1H, 3'-H). [Compound
18 is hereinafter also referred to as COMPOUND "W" or
20  120033]

25

Example 6

6-[2'-(tert-Butyl)dimethylsilyloxy-4'-bromo-5'-methoxy-phenyl]methyl-3,5,5-trimethyl-cyclohex-2-en-1-one (19):

This compound was prepared from isophorone (0.168 g,
5   1.22 mmol) in the manner previously described for enone
13, affording 0.342 g (60%) of the alkylation product (Rf
0.40, 2:1 hexanes/ethyl acetate) as a colorless, oily

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solid. ¹H NMR (400 MHz,CDCl₃) δ0.20 and 0.22 [2s, 2 x 3H, Si(CH₃)₂], 0-99 [s, 9H, SiC(CH₃)₃], 1.00 and 1.02 (2s, 2 x 3H, geminal-CH₃'s), 1.91 (s, 3H, 3-CH₃), 2.18 and 2.28 (ABq, 2H), 2.42 (dd, 1H), 2.82 (dd, 2H), 3.70 (s, 3H, OCH₃), 5.82 (sl d, 1H, 2-H), 6.71 (s, 1H, 6'-H), 6.92 ppm (s, 1H, 3'-H).

1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl) methyl-3,5,5-trimethylcyclohex-2-ene (20):

This compound was prepared from 6-[2'-(tert-butyl) dimethylsilyloxy-4'-bromo-5'-methoxyphenyl]methyl-3,5,5-trimethylcyclohex-2-en-1-one (19) (42.0 mg, 0.090 mmol) in the manner previously described for acetoxy diene 17, affording 18.4 mg (52%) of the acetoxy-diene as a color-less oil. ¹H NMR (400 MHz, CDCl₃) δ 0.87 and 1.11 (2s, 2 x 3H, geminal-CH₃'s), 1.78 (s, 3H, 3-CH₃), 2.26 (s, 3H, acetate-CH₃), 3.83 (s, 3H, OCH₃), 4.03 and 4.58 (2s, 2 x 1H, methylidene-CH₂), 5.82 (s, 1H, 2-H), 6.52 (s, 1H, 6'-H), 7.19 ppm (s, 1H, 3'-H).

8-(2'-Acetoxy-4'-bromo-5'-methoxyphenyl)methyl-5,7,7-trimethylspiro[2,5]oct-4-ene (21):

To a flame-dried 10 mL round-bottomed flask containing 20.0 mg (0.051 mmol) 1-methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl)methyl-3,5,5-trimethylcyclohex-2-ene (20) in 1 mL 1,2-dichloroethane under nitrogen atmosphere at 0°C was added diethylzinc (254 μL of a 1.0 M solution in hexanes, 0.255 mmol, 5.0 equiv). Chloroiodomethane (37 μL, 0.510 mmol, 10.0 equiv) was added dropwise, and the mixture was allowed to warm to room temperature. After 9 h, the reaction mixture was quenched at 0°C with saturated aqueous NH₄Cl, and the reaction mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (20 mL), dried over Na₂SO₄, and concentrated under diminished pressure. Purification by flash column chroma-tography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 20 mg (96%) of the spirocyclopropane as

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a colorless, viscous oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ -0.07 (ddd, 1H, $J$ = 11.0, 9.3, 5.9 Hz, cyclopropyl-H), 0.16 (ddd, 1H, $J$ = 11.5, 9.4, 6.1 Hz, cyclopropyl-H), 0.32 (ddd, 1H, $J$ = 10. 1, 5.8, 5.8 Hz, cyclopropyl-H), 0.43
5 (ddd, 1H, $J$ = 9.8, 6.1, 6.1 Hz, cyclopropyl-H), 1.03 and 1.06 (2s, 2 x 3H, geminal-CH$_3$'s), 1.60 and 1.98 (ABq, 2H, $J_{AB}$ = 17.8 Hz, 6-H), 1.69 (s, 3H, 5-C*H*3), 2.25 (s, 3H, acetate-CH$_3$), 2.39 and 2.65 (d of ABq, 2H, $J_{AB}$ = 13.6 Hz, $J_A$ = 10.0 Hz, $J_B$ = 3.4 Hz, benzylic-CH$_2$), 3.86 (s, 3H,
10 OC*H$_3$*), 4.68 (s, 4-H), 6.69 (s, 1H, 6'-H), 7.18 ppm (s, 1H, 3'-H). [Compound 21 is hereinafter also referred to as COMPOUND "H" or 120299]

Example 7
*cis*-2-[(2'-*tert*-Butyl)dimethylsilyloxy-4'-bromo-5'-
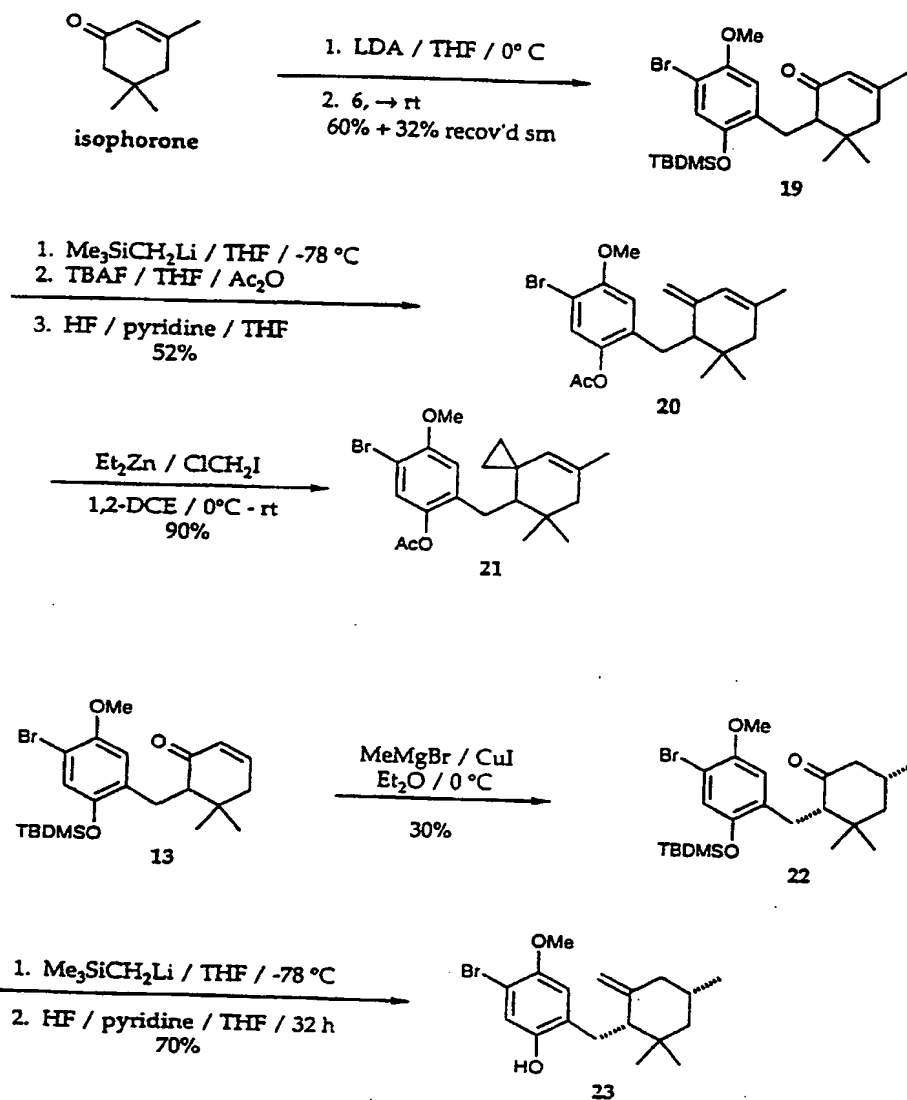15 methoxyphenyl]methyl-3,3,5-trimethylcyclohexan-1-one (22).
     To a suspension of copper(I) iodide (2 mg) in 1 mL of anhydrous ether at 0°C was added methylmagnesium bromide (0.106 mL of a 3.0 M solution in ether, 0.319 mmol, 1.00 equiv). Then enone 13 (149 mg, 0.319 mmol) in 2 mL of
20 anhydrous ether was added slowly to the stirring cuprate mixture at a temperature maintained below 5°C, and upon completion of the addition, the reaction mixture was stirred at 0°C for 3 h before quenching with a 4:1 mixture of saturated aqueous NH$_4$Cl/NH$_4$OH. The resultant biphasic
25 mixture was extracted with ether, dried over Na$_2$SO$_4$, and concentrated under diminished pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 9:1) afforded 36 mg (30%) of the desired conjugate addition product as a white solid. $^1$H NMR (400 MHz,
30 CDCl$_3$) $\delta$ 0.22 (s, 6H, Si(C*H$_3$*)$_2$), 1.00 [m, 18H, 3,3,5-CH$_3$ and SiC(C*H$_3$*)$_3$], 1.50 (dd, 2H, $J$ = 15.1, 6.5 Hz, 4-H), 2.02 (m, 1H, 5-H), 2.14 and 2.23 (ABq, 2H, $J_{AB}$ = 12.0 Hz, 6-H), 2.42 (dd, 1H, $J$ = 10.4, 6.4 Hz, 2-H), 2.88 and 2.89 (d of ABq, 2H, $J_{AB}$ = 12.0 Hz, $J_A$ = 10.4 Hz, $J_B$ = 6.3 Hz, benzylic-CH$_2$),
35 3.82 (s, 3H, OC*H$_3$*), 6.65 (s, 1H, 6'-H), 6.92 ppm (s, 1H, 3'-H).

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<u>cis-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)</u>
<u>methyl-3,3,5-trimethyl-cyclohexane (23):</u>

To a solution of cis-2-[(2'-*tert*-butyl)dimethyl-
silyloxy-4'-bromo-5'-methoxyphenyl]methyl-3,3,5-
5  trimethylcyclohexan-1-one (22) (7.5 mg, 0.016 mmol, 1.0
equiv) in 1 mL of anhydrous THF at -78°C was added
(trimethyl)silylmethyllithium (66 $\mu$L of a 1.0 M solution
in pentane, 0.066 mmol, 4.0 equiv) and the mixture was
stirred for 20 min, at which time TLC analysis indicated
10  complete consumption of starting material, and the reac-
tion was quenched at -78°C with 1 mL of saturated aqueous
NH$_4$Cl solution. The resulting biphasic mixture was allowed
to warm to room temperature and was extracted with ethyl
acetate (30 mL), and the organic layer was dried over
15  Na$_2$SO$_4$, and concentrated under diminished pressure.
Purification by flash column chromatography (silica gel,
hexanes/ethyl acetate, 4:1) afforded 7.3 mg (86%) of the
desired tertiary alcohol intermediate as a colorless oil.
Five milligrams of this intermediate were placed in a 10
20  mL Nalgene vial containing 1 mL of dry THF, 68 $\mu$L of
HF/pyridine complex were added, and the mixture was
allowed to stir at room temperature for 32 h, after which
time the contents of the vial were transferred into a
separatory funnel containing 3 mL of ethyl acetate and 1
25  mL of 1 M aqueous NaHSO$_4$. The layers were separated, and
the organic phase was washed with 1 mL of brine, dried
over Na$_2$SO$_4$, and concentrated under diminished pressure.
Purification by flash column chromatography (silica gel,
hexanes/ethyl acetate, 9:1) afforded 2.7 mg (81 %) of the
30  desired phenol as a colorless, viscous oil. $^1$H NMR (400
MHz, CDCl$_3$) $\delta$ 0.92 and 1.06 (2s, 2 x 3H, geminal-CH$_3$'s),
0.95 (d, 3H, $J$ = 8.0 Hz, 5-CH$_3$), 1.70 (m, 1H), 1.84 (m,
2H), 2.09 (m, 1H), 2.10 (dd, 1H, $J$ = 13.3, 4.2 Hz, 2-H),
2.58 and 2.81 (d of ABq, 2H, $J_{AB}$ = 13.6 Hz, $J_A$ = 11.2 Hz,
35  $J_B$ = 3.7 Hz, benzylic-CH$_2$), 3.81 (s, 3H, OCH$_3$), 4.27 and
4.58 (2s, 2 x 1H, methylidene-CH$_2$), 4.42 (s, 1H, OH), 6.53

29

(s, 1H, 6'-H), 6.94 ppm (s, 1H, 3'-H). [Compound 23 is hereinafter also referred to as COMPOUND "S" or 120275]

30

Example 8

1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)
methyl-3,3-dimethylcyclo-pentane (26) :

This compound was prepared from 4,4-dimethylcyclopent-
5  2-en-1-one (24) and benzylic bromide 6 in 5 steps in the
manner previously described for the synthesis of olefin
16, with the following procedural changes in the last two
steps, from intermediate 25.  To a flame-dried 25 mL
round-bottomed flask containing a magnetic stir bar was
10  added 340 mg (0.90 mmol) of cerium trichloride hepta-
hydrate, and the flask was heated to 140°C under vacuum
for 2 h, after which time the solid was cooled to room
temperature, and 3 mL of anhydrous THF was added.  After
stirring for 2 h at room temperature, the slurry was
15  cooled to -78°C and (trimethyl) silylmethyllithium (0.78
mL of a 1.0 M solution in pentane, 0.78 mmol) was added.
After 30 min, 2-[(2'-tert-butyl)dimethylsilyloxy-4'-bromo-
5'-methoxyphenylmethyl-3,3-dimethylcyclopentanone      25
(15.0 mg, 0.034 mmol) in 1 mL of anhydrous THF was added,
20  and the mixture was allowed to stir at -78°C for 4 h,
before quenching with saturated aqueous $NH_4Cl$.  The reac-
tion mixture was extracted with ether, and the organic
phase was dried over $Na_2SO_4$, and concentrated under
diminished pressure.   Purification by flash column
25  chromatography (silica gel, hexanes/ethyl acetate 9:1)
gave 15 mg (83%) of the tertiary alcohol intermediate as
a colorless oil.  Compound 26 was prepared from this
alcohol intermediate (7.3 mg, 0.014 mmol) in the manner
previously described for the preparation of olefin 16,
30  affording 3.0 mg (66%) of the desired product as a
colorless oil.  $^1$H NMR (400 MHz, $CDCl_3$) δ0.92 and 0.96 (2s,
2 x 3H, geminal-$CH_3$'s), 1.53 (m, 2H, 4-H), 2.39 (m, 3H, 2-H
and 5-H), 2.57 and 2.67 (d of ABq, 2H, benzylic-$CH_2$), 3.81
(s, 3H, $OCH_3$),4.50 (s, 1H, OH), 4.66 and 4.84 (2s, 2 x 1H,
35  methylidene-$CH_2$), 6.74 (s, 1H, 6'-H), 6.99 ppm (s, 1H, 3'-
H).   [Compound 26 is hereinafter also referred to as
COMPOUND "K" or 120192]

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Example 9
2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methylcyclohex-1-
one (28):

This compound was prepared in two steps from cyclo-
5    hexanone and 2-(tert-butyl)dimethylsilyloxy-4-bromo-5-
methoxybenzyl bromide (6) as previously described, to give
the desired olefin in two steps in 50.4% overall yield as
a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 2.49 (dd, 1H,
2H), 2.54 and 2.92 (d of ABq, 2H, benzylic-CH$_2$), 3.83 (s,
10   3H, OCH$_3$), 4.46 (s, 1H, OH), 6.61 (s, 1H, 6'-H), 7.02 ppm
(s, 1H, 3'-H). [Compound 28 is hereinafter also referred
to as COMPOUND "Y" or 120125]


Examples 10-11
(5R,6S)-6-[2'-(tert-Butyl)dimethylsilyloxy-4'-bromo-5'-
15   methoxyphenyl)methyl-5-methylcyclohex-2-en-1-one (29):

To a solution of lithium diisopropylamide (4.65 mL of
a 2.0 M solution in THF, 9.30 mmol, 2.2 equiv) in 15 mL of
anhydrous THF and 4.4 mL of dry hexamethylphosphoramide
(HMPA) at -35°C was added dropwise ketosulfoxide 12 (pre-
20   pared from (R)-(+)-pulegone according to the method of
Oppolzer and Petrzika; Helv. Chim. Acta 1978, 61, 2755) in
5 mL of dry THF. The reaction mixture was stirred at -
35°C for 3 h, after which 2-(tert-butyl)dimethylsilyloxy-
4-bromo-5-methoxybenzyl bromide (6) was added dropwise as
25   a solution in 10 mL of anhydrous THF. The reaction mix-
ture was allowed to stir for an additional 2 h at -35°C,
quenched with 1M aqueous NaHSO$_4$ (15 mL) and extracted with
ether (50 mL). The organic layer was washed with water (3
x 15mL) and brine (1 x 15 mL), then dried over Na$_2$SO$_4$ and
30   concentrated under diminished pressure to afford 2.37g of
the intermediate ketosulfoxide as a pale yellow oil, which
was used directly in the next step without purification.
A solution of the intermediate ketosulfoxide (2.37 g, 4.20
mmol) and CaCO$_3$ (0.40 g, 3.90 mmol) in 90 mL of carbon
35   tetrachloride was brought to reflux for 3 h. Upon cooling
to room temperature, the reaction mixture was filtered and

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the solvent was removed under diminished pressure.
Purification by flash column chromatography (silica gel,
hexanes/ethyl acetate, 95:5) afforded 550 mg (30%) of the
desired enone. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.18 and 0.22

5  [2s, 2 x 3H, Si(CH$_3$)$_2$], 1.03 [s, 9H, SiC(CH$_3$)$_3$], 1.05 (d,
3H, $J$ = 8.0 Hz, 5-C$H_3$), 2.07 (m, 2H), 2.50 (m, 1H, 6-H),
2.65 (m, 1H), 2.91 (m, 2H, benzylic-CH$_2$), 3.80 (s, 3H,
OC$H_3$), 6.02 (d, 1H, $J$ = 9.4 Hz, 2-H), 6.70 (s, 1H, 6'-H),
6.85 (ddd, 1H, $J$ = 9.6, 4.1, 3.2 Hz, 3-H), 6.98 ppm (s,

10  1H, 3'-H).


(5*R*,6*S*)-1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxy-
phenyl)methyl-5-methylcyclohex-2-ene (30):

To a solution of (5*R*,6*S*)-6-[(2'-*tert*-butyl)dimethyl-
silyloxy-4'-bromo-5'-methoxyphenyl)methyl-5-methylcyclo-

15  hex-2-en-1-one (29) (63 mg, 0.139 mmol, 1.00 equiv) in 2
mL of anhydrous THF at -78°C was added (trimethyl)silyl-
methyllithium (222 μL of a 1.0 M solution in pentane,
0.222 mmol, 1.60 equiv). After 10 minutes of stirring at
-78°C, the reaction was quenched at -78°C with 1 mL of

20  saturated aqueous NH$_4$Cl. The reaction mixture was
extracted with ethyl acetate, dried over Na$_2$SO$_4$ and
concentrated under diminished pressure. Purification by
flash column chromatography (silica gel, hexanes/ethyl
acetate, 95:5) afforded 40.5 mg (60%) of the desired

25  tertiary alcohol intermediate, along with 14 mg (22%) of
unreacted starting material. This intermediate alcohol
(14 mg, 0.028 mmol) was dissolved in 1 mL of anhydrous THF
containing 60 mL (0.56 mmol, 20.0 equiv) of acetic
anhydride, and cooled to 0°C. Tetra-(*n*-butyl)ammonium

30  fluoride (33 μL of a 1.0 M solution in THF, 0.033 mmol,
1.20 equiv) was added, and the mixture was allowed to warm
to room temperature. The contents of the flask were then
poured into a separatory funnel containing 5 mL of ethyl
acetate and 2 mL of aqueous 1 M NaHSO$_4$. The layers were

35  separated, the organic phase was dried over Na$_2$SO$_4$, and the
solvent was removed under diminished pressure. The crude

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intermediate (12.4 mg) was placed in a 10 mL Nalgene vial containing 2 mL of dry THF, 0.175 mL of premade HF/pyridine complex was added, and the mixture was allowed to stir at room temperature for 18 h. The contents of the
5   vial were then transferred into a separatory funnel containing 5 mL of ethyl acetate and 3 mL of aqueous 1 M NaHSO$_4$. The layers were separated, and the organic phase was washed with 2 mL of brine, dried over Na$_2$SO$_4$, and concentrated under diminished pressure. Purification by
10  flash column chromatography (silica gel, hexanes/ethyl acetate, 85:15) afforded 6.4 mg (60% for the 2 steps) of the desired acetylated phenol. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.85 (d, 3H, 5-CH$_3$), 1.67 (m, 2H), 1.76 (s, 3H, 3-CH$_3$), 2.20 (dd, 1H), 2.27 (s, 3H, acetate-CH$_3$), 2.49 (m, 3H),
15  3.86 (s, 3H, OCH$_3$), 4.40 and 4.71 (2s, 2 x 1H, methylidene-CH$_2$), 5.86 (s, 1H, 3-H), 6.64 (s, 1H, 6'-H), 7.21 ppm (s, 1H, 3'-H). [Compound 30 is hereinafter also referred to as COMPOUND "L" or 120260]


(5*R*,6*S*)-6-[2'-(*tert*-Butyl)dimethylsilyloxy-4'-bromo-5'-
20  methoxyphenyl)methyl-3,5-dimethylcyclohex-2-en-1-one (31):
     To a suspension of copper(I) iodide (1.36 mg) in 0.5 mL of anhydrous ether at 0°C was added methylmagnesium bromide (222 $\mu$L of a 310 M solution in ether, 0.665 mmol, 1.00 equiv), causing the solution to turn dark. A solu-
25  tion of enone (29) (310 mg, 0.665 mmol) in 1 mL of anhydrous ether was added over a period of 2 minutes keeping the temperature below 5°C. After the addition was complete, the mixture was stirred at 0°C for an additional 30 minutes, at which time phenylselenenyl bromide (157 mg,
30  0.665 mmol) in 0.5 mL of anhydrous THF was added, keeping the temperature below 10°C. The resulting mixture was stirred for 10 minutes, poured into water (2 mL) and extracted with ether (5 mL). The organic phase was washed twice with water (2 mL), dried over Na$_2$SO$_4$ and concentrated
35  under diminished pressure. The resultant oil was dissolved in 2 mL of dry dichloromethane and 162

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μL of pyridine, and to this a solution of hydrogen
peroxide 35% (181 μL) in 162 mL of water was added
dropwise, keeping the temperature between 30-35°C and
warming if necessary to initiate the reaction. The
5   mixture was stirred at room temperature for 30 minutes,
and then poured into a separatory funnel containing
dichloromethane-saturated aqueous NaHCO₃. After extraction
of the mixture with dichloromethane, the organic solution
was washed successively with 10% aqueous HCl and brine,
10   and dried over Na₂SO₄. The solvent was removed under
diminished pressure, and the residue was purified by flash
column chromatography (silica gel, hexanes/ethyl acetate,
9:1), affording 157 mg (60%) of the desired enone as a
colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.15 and 0.20
15   [2s, 2 x 3H, Si(CH₃)₂], 0.97 [s, 9H, SiC(CH₃)₃], 0.95 (d,
3H, J = 8.0 Hz, 5-CH₃), 1.90 (s, 3H, 3-CH₃), 1.95 (m, 2H),
2.38 (m, 1H), 2.59 (m, 1H, 6-H), 2.87 (m, 2H, benzylic-
CH₂), 3.79 (s, 3H, OCH₃), 5.86 (s, 1H, 2-H), 6.69 (s, 1H,
6'-H), 6.96 ppm (s, 1H, 3'-H).

20   <u>(5R,6S)-1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxy-
phenyl)methyl-3,5-dimethyl-cyclohex-2-ene (32)</u>:
      To a solution of (5R,6S)-6-[2'-(tert-butyl)dimethyl-
silyloxy-4'-bromo-5'-methoxyphenyl)methyl-3,5-dimethyl-
cyclohex-2-en-1-one (31) (63 mg, 0.139 mmol, 1.0 equiv) in
25   2 mL of anhydrous THF at -78°C was added (trimethyl)
silylmethyllithium (222 μL of a 1.0 M solution in pentane,
0.222 mmol, 1.60 equiv). After 10 minutes of stirring at
-78°C, the reaction was quenched at -78°C with 1 mL of
saturated aqueous NH₄Cl. The reaction mixture was
30   extracted with ethyl acetate, dried over Na₂SO₄, and the
solvent was removed under diminished pressure.
Purification by flash column chromatography (silica gel,
hexanes/ethyl acetate, 95:5), afforded 40.5 mg (60%) of
the desired tertiary alcohol intermediate, along with 14
35   mg (22%) of unreacted starting material. This intermedi-
ate alcohol (14 mg, 0.028 mmol) was dissolved in 1 mL of

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anhydrous THF containing 60 μL (0.56 mmol, 20.0 equiv) of acetic anhydride and cooled to 0°C. Tetra-(n-butyl) ammonium fluoride (33 μL of a 1.0 M solution in THF, 0.033 mmol, 1.2 equiv) was added, and the mixture was allowed to
5    warm to room temperature. The contents of the flask were poured into a separatory funnel containing 5 mL of ethyl acetate and 2 mL of aqueous 1 M NaHSO$_4$. The layers were separated, and the organic phase was dried over Na$_2$SO$_4$. The solvent was removed under diminished pressure, and the
10   crude intermediate (12.4 mg) was placed in a 10 mL Nalgene vial containing 2 mL of dry THF, 0.175 mL of HF/pyridine complex was added, and the mixture was allowed to stir at room temperature for 18 h. The contents of the vial were transferred to a separatory funnel containing 5 mL of
15   ethyl acetate and 3 mL of 1 M aqueous NaHSO$_4$, the layers were separated, and the organic phase was washed with 2 mL of brine, dried over Na$_2$SO$_4$, and the solvent was removed under diminished pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 85:15)
20   afforded 6.4 mg (60% for 2 steps) of the desired acetylated phenol as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.85 (d, 3H, 5-CH$_3$), 1.67 (m, 2H), 1.76 (s, 3H, 3-CH$_3$), 2.20 (dd, 1H), 2.27 (s, 3H, acetate-CH$_3$), 2.49 (m, 3H), 3.86 (s, 3H, OCH$_3$), 4.40 and 4.71 (2s, 2 x 1H,
25   methylidene-CH$_2$), 5.86 (s, 1H, 3-H), 6.64 (s, 1H, 6'-H), 7.21 ppm (s, 1H, 3'-H). [Compound 32 is hereinafter also referred to as COMPOUND "O" or 120276]

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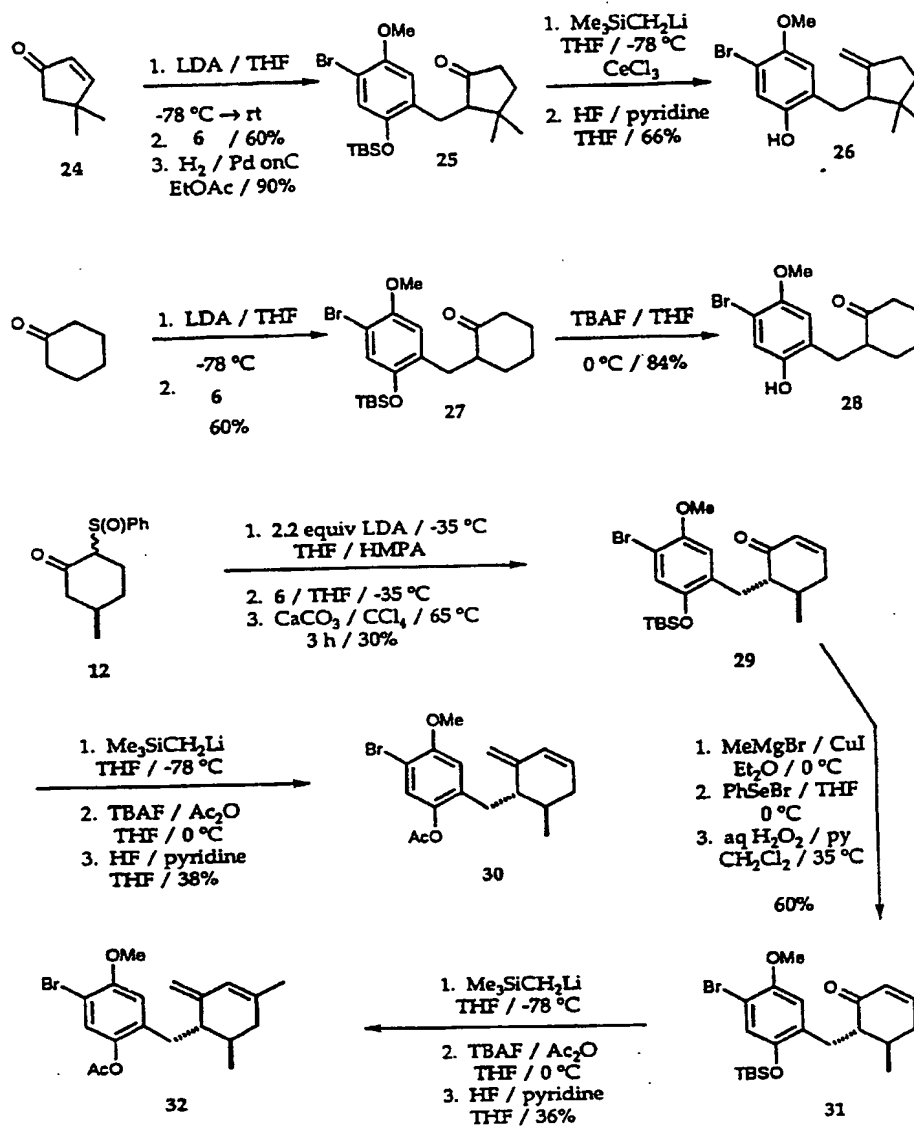


## Example 12

<u>1-Methylidene-6-(2'-hydroxyphenyl)methyl-5,5-dimethyl-</u>
<u>cyclohex-2-ene (34)</u>:

     This compound was prepared from 5,5-dimethylcyclohex-
5  2-en-1-one (11) and 2-(*tert*-butyl)dimethylsilyloxybenzyl

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bromide (9) in three steps in the manner previously described for the synthesis of olefin 16, affording the desired phenol as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$)

δ 0.90 and 1.15 (2s, 2 x 3H, geminal-CH$_3$'s), 1.85 and 2.24

5 (d of ABq, 2H, $J_{AB}$ = 18.8 Hz, $J_A$ = 5.5 Hz, $J_B$ = 0 Hz, 4-H), 2.06 (dd, 1H, $J$ = 11.4, 3.2 Hz, 6-H), 2.30 and 2.88 (d of ABq, 2H, $J_{AB}$ = 13.5 Hz, $J_A$ = 11.4 Hz, $J_B$ = 3.4 Hz, benzylic-CH$_2$), 4.20 and 4.69 (2s, 2 x 1H, methylidene-CH$_2$), 4.61 (s, 1H, O$H$), 5.77 (ddd, 1H, $J$ = 7.8, 5.4, 5.4 Hz, 3-H), 6.09

10 (dd, 1H, $J$ =, 7.5, 2.2 Hz, 2-H), 6.75 (dd, 1H, $J$ = 7.1, 0.8 Hz, 3'-H), 6.82 (ddd, 1H, $J$ = 8.4, 7.3, 1.1 Hz, 5'-H), 6.97 (dd, 1H, $J$ = 5.9, 1.5 Hz, 6'-H), 7.05 ppm (ddd, 1H, $J$ = 9.3, 7.8, 1.7 Hz, 4'-H). [Compound 34 is hereinafter also referred to as COMPOUND "C" or 120363]

15 Example 13

1-Methylidene-2-(2'-hydroxyphenyl)methyl-5.5-dimethylcyclohexane (35):

This compound was prepared from 5,5-dimethylcyclohex-2-en-1-one (11) and 2-(tert-butyl)dimethylsilyloxybenzyl

20 bromide (9) in four steps in the manner previously described for the synthesis of olefin 16, affording the desired olefin as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.97 and 1.01 (2s, 2 x 3H, geminal-CH$_3$'s), 2.09 (ddd, 1H) and 2.27 (ddd, 1H) [6-H], 2.18 (dd, 1H, 2-$H$), 2.70 and

25 2.84 (d of ABq, 2H, benzylic-CH$_2$), 4.37 (sl d, 1H) and 4.63 (s, 1H) [methylidene-CH$_2$], 4.72 (s, 1H, O$H$), 6.72 (d, 1H, 3'-H), 6.81 (dd, 1H, 5'-H), 7.03 (d, 1H, 6'-H), 7.04 ppm (dd, 1H, 4'-H). [Compound 35 is hereinafter referred to as COMPOUND "D" or 120370]
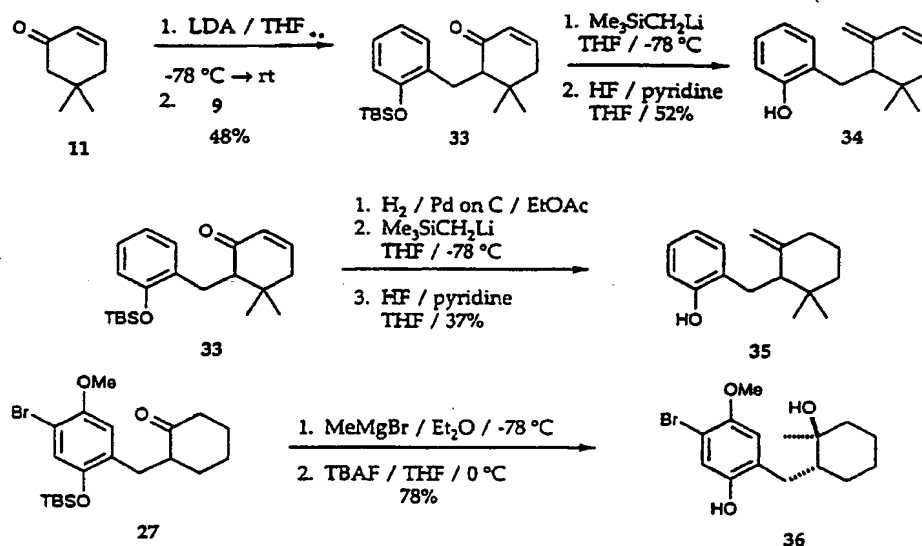
30 Example 14

trans-1-Methyl-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl) methylcyclohexan-1-ol (36):

To a solution of 2-[(2'-tert-butyl)dimethylsilyloxy-4'-bromo-5'-methoxyphenyl] methylcyclohexan-1-one (27) (10

35 mg, 0.023 mmol) in 1 mL of anhydrous ether at -78°C was

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added methylmagnesium bromide (8.0 $\mu$L of a 3.0 M solution
in ether, 0.024 mmol, 1.06 equiv). The reaction mixture
was stirred at -78°C for 30 minutes and quenched with
saturated aqueous $NH_4Cl$, extracted with ether, and the
5   organic phase was dried over $Na_2SO_4$ and concentrated under
diminished pressure. Purification by flash column
chromatography (silica gel, hexanes/ethyl acetate, 4:1)
gave 10 mg (97%) of the desired tertiary alcohol as a
colorless oil. To a solution of 10 mg (0.021 mmol) of
10  this tertiary alcohol in 1 mL of dry THF at 0 °C was added
tetra-(n-butyl)ammonium fluoride (25 $\mu$L of a 1.0 M
solution in THF, 0.025 mmol, 1.2 equiv), and the reaction
mixture was allowed to stir for 20 minutes, then diluted
with water, and extracted with ethyl acetate. The organic
15  phase was washed with brine, dried over $Na_2SO_4$ and
concentrated under diminished pressure. Purification by
flash column chromatography (silica gel, hexanes/ethyl
acetate, 4:1) gave 6 mg (80%) of the desired tertiary
alcohol as a colorless, viscous oil. $^1H$ NMR (400 MHz,
20  $CDCl_3$) $\delta$ 1.32 (s, 3H, $CH_3$), 2.45 and 2.93 (d of ABq, 2H,
benzylic-$CH_2$), 3.83 (s, 3H, $OCH_3$), 6.61 (s, 1H, 6'-H), 7.04
ppm (s, 1H, 3'-H). [Compound 36 is hereinafter also
referred to as COMPOUND "Q" or 120136]

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Example 15

1-Methylidene-6-(3'-nitrophenyl)methyl-5,5-dimethylcyclo-
hex-2-ene (38):

      This compound was prepared from 5,5-dimethylcyclohex-
5  2-en-1-one (11) (0.150 g, 1.21 mmol) and *m*-nitrobenzyl
   bromide (0.510 g, 2.42 mmol, 2.00 equiv) in three steps in
   the manner previously described for the synthesis of
   olefin 16, affording 42.7 mg (26% overall), of the nitro-
   diene as a pale yellow oil.  $^1$H NMR (400 MHz, CDCl$_3$)  δ 0.91
10  and 1.13 (2s, 2 x 3H, geminal-CH$_3$'s), 1.99 and 2.12 (d of
   ABq, 2H, benzylic-CH$_2$), 4.07 and 4.89 (2s, 2 x 1H, methyli-
   dene-CH$_2$),5.77 and 6.00 (2dd, 2 x 1H, 2,3-H), 7.42 (dd, 1H,
   Ar-H), 7.59 (d, 1H, Ar-H), 7.96 (d, 1H, Ar-H), 8.00 ppm
   (s, 1H, Ar-H). [Compound 38 is hereinafter also referred
15  to as COMPOUND "A" or 120117]

40

## Example 16

### 6-(4'-Nitrophenyl)methyl-5,5-dimethylcyclohex-2-en-1-one (39):

This compound was prepared from 5,5-dimethylcyclohex-
2-en-1-one (11) (0.600 g, 4.83 mmol) and *p*-nitrobenzyl
bromide (1.581 g, 7.32 mmol) in the manner previously
described for the synthesis of enone 13, affording 627 mg
(50%), of the nitro-enone as a pale yellow oil.  $^1$H NMR
(400 MHz, CDCl$_3$) $\delta$ 1.02 and 1.18 (2s, 2 x 3H, geminal-
CH3's), 2.83 and 3.10 (d of ABq, 2H, benzylic-CH$_2$), 6.00
(ddd, 1H, 2-H), 6.81 (ddd, 1H, 3-H), 7.38 and 8.10 ppm
(ABq, 2 x 2H, Ar-H).

### 2-(4'-Nitrophenyl)methyl-3,3-dimethylcyclohexan-1-one (40):

An atmosphere of hydrogen was introduced to and
maintained by a balloon to an evacuated 50 mL round-
bottomed flask containing 6-(4'-nitrophenyl)methyl-5,5-
dimethylcyclohex-2-en-1-one (39) (14.0 mg, mmol) and
tris(triphenylphosphine)rhodium chloride (Wilkinson's
catalyst) (8.0 mg) in 6.5 mL anhydrous benzene. The
yellow-orange solution was stirred at room temperature for
24 h, and then passed through a short silica gel column
(hexanes/ethyl acetate, 3:1) to afford the 6.8 mg (48%) of
the desired ketone as a pale yellow oil (Rf 0.43, 2:1
hexanes/ethyl acetate).  $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.86 and
1.23 (2s, 2 x 3H, geminal-CH$_3$'s), 2.50 (d, 1H, $J$ = 13.0 Hz,
2-H), 2.66 and 3.17 (d of ABq, 2H, $J_{AB}$ = 13.0 Hz, $J_A$ = 1.6
Hz, $J_B$ = 9.6 Hz, benzylic-CH$_2$), 7.37 (d, 2H, $J$ = 9.6 Hz,
2',6'-H), 8.09 ppm, (d, 2H, $J$ = 9.6 Hz, 3',5'-H).
[Compound 40 is hereinafter also referred to as COMPOUND
"V" or 120211]

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<u>Example 17</u>
<u>1-Methylidene-6-(3'-methyl-4'-nitrophenyl)methyl-5,5-</u>
<u>dimethylcyclohex-2-ene (41):</u>
This compound was prepared from 6-(4'-nitrophenyl)
5   methyl-5,5-dimethylcyclohex-2-en-1-one (39) (133 mg, 0.514
mmol) in the manner previously described for the synthesis
of olefin 16, with the following procedural changes.
Three equivalents of (trimethyl)silylmethyllithium were
used, and the subsequent elimination step required 48 h to
10   go to completion, affording 120 mg (86%) of the nitro-
diene as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.92
and 1.12 (2s, 2 x 3H, geminal-CH$_3$'s), 2.58 (s, 3H, Ar-CH$_3$),
4.05 and 4.64 (2s, 2 x 1H, methylidene-CH$_2$), 5.70 (ddd, 1H,
3-H), 6.03 (dd, 1H, 2-H), 6.98 (s, 1H, Ar-H), 6.99 and
15   7.88 ppm (2d, 2 x 1H, Ar-H). [Compound 41 is hereinafter
also referred to as COMPOUND "T" or 120120]

<u>Example 18</u>
<u>6-(4'-Nitrophenyl)methyl-3,5,5-trimethylcyclohex-2-en-1-</u>
<u>one (42):</u>
20   This compound was prepared from isophorone (2.065 g,
14.94 mmol) and p-nitrobenzyl bromide (4.06 g, 18.80 mmol,
1.25 equiv) in the manner previously described for the
synthesis of enone 13, affording 1.891 g (46%), of the
nitro-enone as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$)
25   $\delta$ 0.98 and 1.13 (2s, 2 x 3H, geminal-CH$_3$'s), 1.92 (s, 3H,
3-CH$_3$), 2.17 and 2.31 (ABq, 2H, $J_{AB}$ = 18.5 Hz, 4-H), 2.38
(dd, 1H, J = 9.0, 3.3 Hz, 6-H), 2.75 and 3.05 (d of ABq,
2H, $J_{AB}$ = 14.0 Hz, $J_A$ = 3.2 Hz, $J_B$ = 8.9 Hz, benzylic-CH$_2$),
5.84 (s, 1H, 2-H), 7.33 (d, 2H, J = 8.2 Hz, Ar-H) and 7.53
30   ppm (d, 2H, J = 8.2 Hz, Ar-H).

<u>1-Methylidene-6-(3'-methyl-4'-nitrophenyl)methyl-3,5,5-</u>
<u>trimethylcyclohex-2-ene (43):</u>
This compound was prepared from 6-(4'-nitrophenyl)
methyl-3,5,5-trimethylcyclohex-2-en-1-one (42) (21.0 mg,
35   0.077 mmol) in the manner previously described for the

42

synthesis of olefin 16, using three equivalents of (trimethyl)silylmethyllithium, and allowing 18 h for the subsequent elimination step, affording 3.5 mg (16%) of the nitro-diene as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.89 and 1.15 (2s, 2 x 3H, geminal-CH$_3$'s), 1.96 and 2.10 (ABq, 2H, benzylic-CH$_2$), 2.58 (s, 3H, Ar-CH$_3$), 2.92 (dd, 1 H, 6-H), 3.96 and 4.54 (2s, 2 x 1H, methylidene-CH$_2$), 5.82 (s, 1H, 2-H), 6.98 (s, 1H, Ar-H), 6.99 and 7.88 ppm (2d, 2 x 1H, Ar-H). [Compound 43 is hereinafter also referred to as COMPOUND "U" or 120168]

Examples 19-20
2-(4'-Nitrophenyl)methylcyclohexan-1-one (44):
    To a solution of diisopropylamine (342 μL, 2.45 mmol, 1.2 equiv) in 5 mL of anhydrous THF at 0°C was added n-butyllithium (1.63 mL of a 1.6 M solution in hexane), and the mixture was stirred at this temperature for 15 minutes before cooling to -78°C. Cyclohexanone (221 μL, 2.04 mmol, 1.0 equiv) in 2 mL of anhydrous THF was then added dropwise, stirred at -78°C for 1 h followed by p-nitrobenzyl bromide (880 mg, 4.08 mmol, 2.00 equiv) in 2 mL of THF, added dropwise to the resulting enolate. The reaction mixture was stirred at room temperature for 17 h, and then quenched with aqueous saturated NH$_4$Cl, and extracted with ether. The organic phase was dried over Na$_2$SO$_4$ and concentrated under diminished pressure to a solid residue that was purified by flash chromatography (silica gel, hexanes / ethyl acetate, 85:15), which afforded 300 mg (64%) of the desired ketone as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.41 (m, 1H), 1.66 (m, 2H), 1.88 (m, 1H), 2.08 (m, 2H), 2.33 (m, 1H), 2.45 (m, 1H), 2.57 (m, 1H, 2-H), 2.59 and 3.29 (d of ABq, 2H, benzylic-CH$_2$), 7.34 (d, 2H, Ar-H), 8.12 ppm (d, 2H, Ar-H). [Compound 44 is hereinafter also referred to as COMPOUND "G" or 120138]

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*trans*-2-(4'-Nitrolphenyl)methylcyclohexan-1-ol (45):

To a stirring solution of 2-(4'-nitrobenzene) methylcyclohexan-1-one (44) in 5 mL of methanol at 0°C was added portionwise sodium borohydride, and the reaction mixture was allowed to stir at 0°C for 1.5 h before quenching with saturated aqueous $NH_4Cl$. The methanol was removed under diminished pressure, and the resultant aqueous residue was extracted with ethyl acetate. The organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated under diminished pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 4:1) gave 10 mg (20%) of the desired alcohol 45, along with 18 mg (36%) of the diastereoisomeric alcohol 46 as colorless oils. Data for alcohol 45: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (m, 1H), 1.11 (m, 1H), 1.28 (m, 3H), 1.60 (m, 2H), 1.76 (m, 1H), 2.02 (m, 1H, 2-H), 2.51 and 3.59 (d of ABq, 2H, benzylic-$CH_2$), 3.27 (m, 1H, 1-H), 7.34 (d, 2H, Ar-H), 8.15 ppm (d, 2H, Ar-H). [Compound 45 is hereinafter also referred to as COMPOUND "I" or 120154.]

44
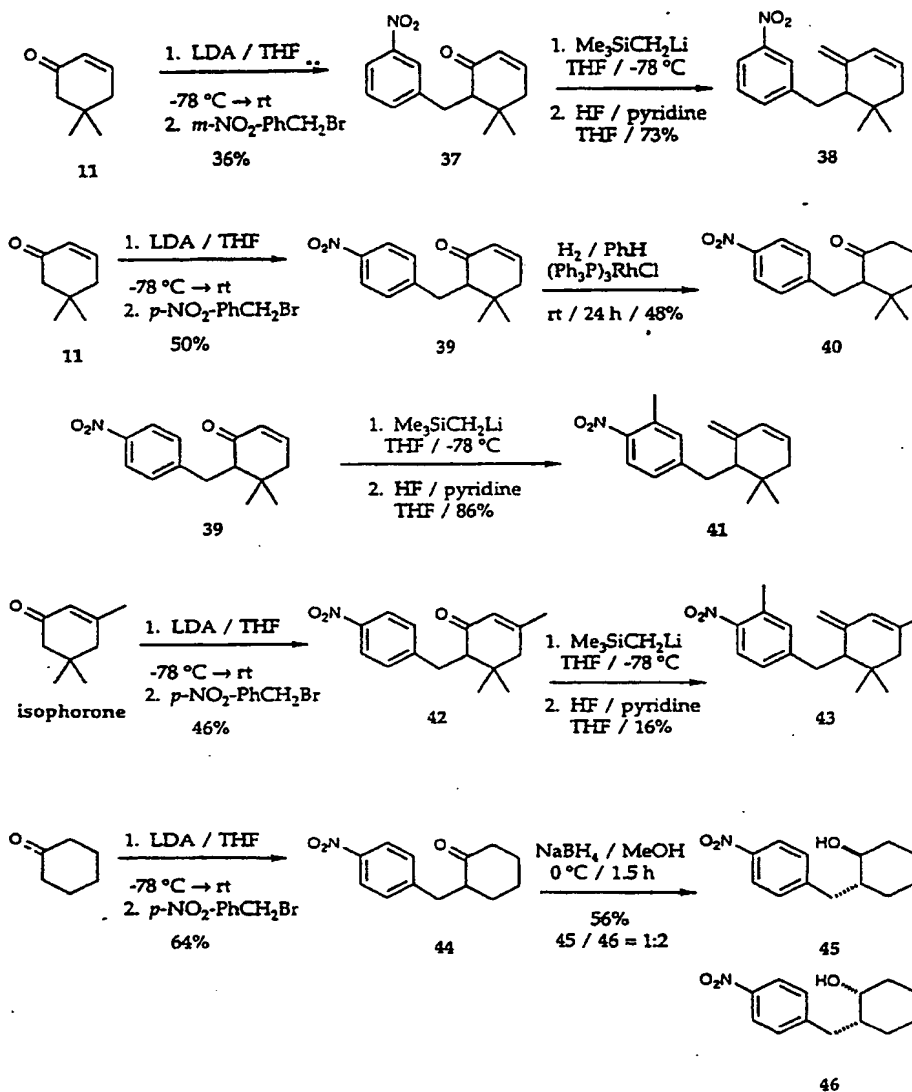
Example 21

(2R)-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-3,3-dimethyl-cyclohexane (49):

    To a flame-dried 10 mL round-bottomed flask containing
5   (1S,3R)-4-methylidene-1-bromo-3-[2'(tert-butyl)dimethyl-
silyloxy-4'-bromo-5'-methoxyphenyl]methyl-2,2-dimethyl-

45

cyclohexane (47) (19.5 mg, 0.036 mmol) in 1 mL anhydrous
benzene with 2 mg AIBN at room temperature was added n-
Bu$_3$SnH (39 μL, 0.144 mmol, 4.0 equiv). After 90 min, TLC
analysis indicated virtually complete consumption of
5    starting material, and formation of a slightly less polar
product. Carbon tetrachloride (200 μL) was added, and
after 1 h at room temperature followed by 1.5 h at 0°C, 2
mL THF and 200 μL 1.0 M tetra-(n-butyl)ammonium fluoride
solution in THF were added. After 10 min at 0°C, pH 7
10   buffer was added, and the reaction mixture was extracted
with hexanes. The resultant organic solution was dried
over Na$_2$SO$_4$, and concentrated under diminished pressure.
Purification by flash column chromatography (silica gel,
10% ethyl acetate in hexanes) afforded 7.5 mg (61%) of the
15   debromophenol as a colorless oil. The 400 MHz $^1$H NMR
spectrum and TLC elution properties of this compound were
identical to those reported for the racemic compound.
[Compound 49 is hereinafter also referred to as COMPOUND
"N" or 120037]

20   Example 22
      (2S)-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-3,3-dimethyl-cyclohexane (52):
      This compound was prepared from (1S,3S)-4-methylidene-
1-bromo-3-[2'-(tert-butyl)dimethylsilyloxy-4'-bromo-5'-
25   methoxyphenyl]methyl-2,2-dimethylcyclohexane (50) (25.0
mg, 0.047 mmol) in the manner described for the synthesis
of derivative 49, affording 5.5 mg (35%) of the
debromophenol as a colorless oil, along with the remainder
of the mass balance as deprotected starting material. The
30   400 MHz $^1$H NMR spectrum and TLC elution properties of this
compound were identical to those reported for the racemic
compound. [Compound 52 is hereinafter also referred to as
COMPOUND "X" or 120158]

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## Example 23

### (1S,3S,5S)-4-Methylidene-1-bromo-5-hydroxy-3-(2'-acetoxy-4'-bromo-5'-methyoxyphenyl)methyl-2,2-dimethylcyclohexane (54):

5      To a flame-dried 25 mL round-bottomed flask containing (1S,3S)-4-methylidene-1-bromo-3-(2'-acetoxy-4'-bromo-5'-methyoxyphenyl)methyl-2,2-dimethylcyclohexane (53) (22.8 mg, 0.050 mmol) in 2.5 mL anhydrous dichloromethane at room temperature was added selenium dioxide (5.5 mg, 0.050
10    mmol, 1.00 equiv) and anhydrous t-butyl hydroperoxide (60 μL of a 3.0 M solution in 2,2,4-trimethylpentane, 1.00 mmol, 2.00 equiv), and the mixture was allowed to stir at room temperature for 48 h, at which time the solvent was removed by rotary evaporation. Purification by flash
15    column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 20 mg (84%) of the hydroxy-cyclocymopol acetate as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.94 and 1.24 (2s, 2 x 3H, geminal-CH$_3$'s), 2.23 and 2.41 (dd of ABq, 2H, $J_{AB}$ = 14.0 Hz, $J_A$ = 11.7, 3.5 Hz,
20    $J_B$ = 4.2, 4.2 Hz, 6-H), 2.32 (s, 3H, acetate-CH$_3$), 2.73 and 2.86 (dd of ABq, 2H, $J_{AB}$ = 15.2 Hz, $J_A$ = 11.3, 0.5 Hz, $J_B$ = 15.3, 3.0 Hz, benzylic-CH$_2$), 3.84 (s, 3H, OCH$_3$), 4.31 (br s, 1H, 1-H), 4.55 (dd, 1H, $J$ = 11.7, 4.4 Hz, 5-H), 4.69 and 5.03 (2s, 2 x 1H, methylidene-CH$_2$),6.75 (s, 1H, 6'-H),
25    7.19 ppm (s, 1H, 3'-H).

### (4S,6S)-1-Methylidene-4-bromo-5-(2'-acetoxy-4'-bromo-5'-methyoxyphenyl)methyl-5,5-dimethylcyclohex-2-ene (55):

      To a flame-dried 10 mL round-bottomed flask containing (1S,3S,5S)-4-methylidene-1-bromo-5-hydroxy-3-(2'-acetoxy-
30    4'-bromo-5'-methyoxyphenyl)methyl-2,2-dimethylcyclohexane (54) (6.8 mg, 0.014 mmol) in 2 mL anhydrous benzene at room temperature was added Burgess reagent [(methoxycar-bonylsulfamoyl)triethylammonium hydroxide, inner salt] (8.5 mg, 0.036 mmol, 2.5 equiv), and the mixture was
35    allowed to stir for 12 h. Removal of the solvent under diminished pressure, followed by purification by flash

47

column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 4.8 mg (74%) of the desired diene as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.94 and 1.18 (2s, 2 x 3H, geminal-CH$_3$'s), 2.33 (s, 3H, acetate-
5   CH$_3$), 3.78 (s, 3H, OCH$_3$), 4.69 and 4.78 (2s, 2 x 1H, methylidene-CH$_2$), 5.44 and 5.50 (2dd, 2 x 1H, 5.6-H), 6.64 (s, 1H, 6'-H), 7.00 ppm (s, 1H, 3'-H). [Compound 55 is hereinafter also referred to as COMPOUND "E" or 120261]

48
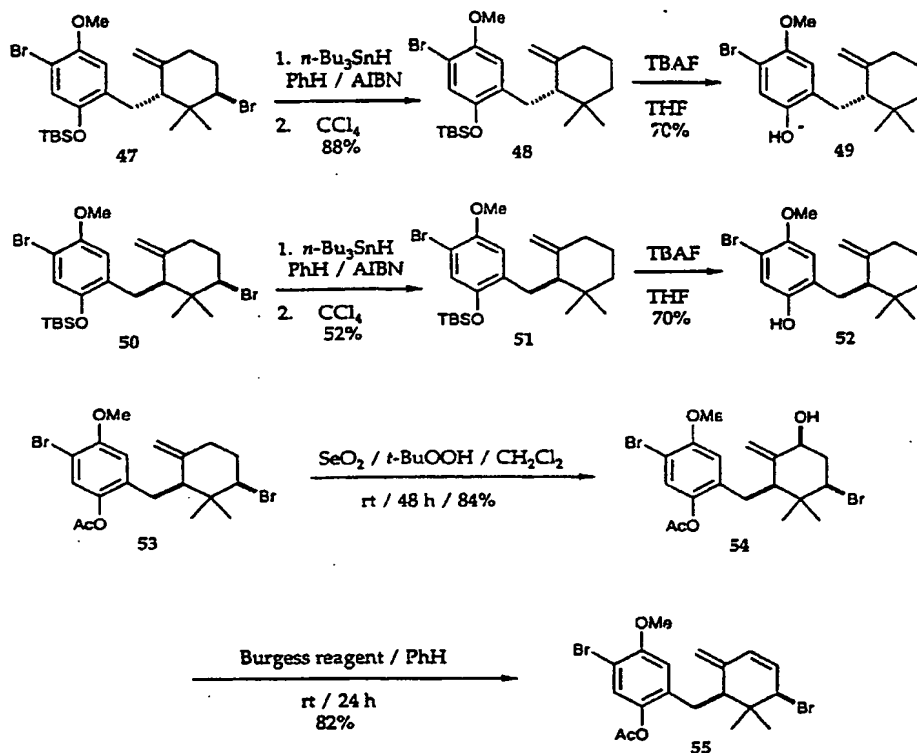
Example 24

(1R,3R)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethylcyclohexane (56) and (1S,3R)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-
5  methoxyphenyl)methyl-4,4-dimethylcyclohexane (57):

This set of diastereomeric alcohols was prepared from (2R)-1-methylidene-2-[2'-(tert-butyl)dimethylsilyloxy-4'-bromo-5'-methoxyphenylmethyl-3,3-dimethylcyclohexane (48) (0.750 g, 1.66 mmol) in the manner previously described
10  for the synthesis of alcohol 54, affording 741 mg (95%) of an inseparable 1:1 mixture of diastereomeric allylic alcohols. A portion (40 mg, 0.085 mmol) of this diastereomeric mixture was subjected to deprotection of the silylphenol in the usual manner, yielding mixture of free
15  phenols, separable by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution), to give 14.0 mg (46%) of the less polar 1R,3R diastereomer (56), along with 13.0 mg (43%) of the more polar 1S,3R diastereomer (57) as white solids. Data for 56: $^1$H NMR (400
20  MHz, CDCl$_3$) $\delta$ 0.93 and 1.12 (2s, 2 x 3H, geminal-CH$_3$'s), 1.70 (m, 2H, 1-H), 1.94 (m, 3H, 6,3-H), 2.65 and 3.00 (d of ABq, 2H, $J_{AB}$ = 14.0 Hz, $J_A$ = 3.1 Hz, $J_B$ = 14.0 Hz, benzylic-CH$_2$) 3.84 (s, 3H, OCH$_3$), 4.37 (br s, 1H, 5-H), 4.39 and 4.92 (2s, 2 x 1H, methylidene-CH$_2$), 6.58 (s, 1H,
25  6'-H), 7.02 ppm (s, 1H, 3'-H). Data for 57: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.00 and 1.02 (2s, 2 x 3H, geminal-CH$_3$'s), 2.45 (dd, 1H, $J$ = 11.5, 3.2 Hz, 3-H), 2.70 and 2.88 (d of ABq, 2H, $J_{AB}$ = 14.1 Hz, $J_A$ = 13.1 Hz, $J_B$ = 4.2 Hz, benzylic-CH$_2$) 3.80 (s, 3H, OCH$_3$), 4.40 (br dd, 1H, $J$ _ 11.5, 4.5 Hz,
30  5-H), 4.47 and 4.86 (2s, 2 x 1 H, methylidene -CH$_2$), 6.61 (s, 1H, 6'-H), 7.94 ppm (s, 1H, 3'-H). [Compound 56 is hereinafter also referred to as COMPOUND "R" or 120243]

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Example 25

(1*S*,3*S*)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethylcyclohexane    (59)    and (1*R*,3*S*)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'

5   methoxyphenyl)methyl-4,4-dimethylcyclohexane (60):

This set of diastereomeric alcohols was prepared from (2*S*)-1-methylidene-2-[2'-(*tert*-butyl)dimethylsilyloxy-4'-bromo-5'-methoxyphenyl]methyl-3,3-dimethylcyclohexane (51) (0.340 g, 0.75 mmol) in the manner previously described

10  for the synthesis of alcohol 54, affording 302 mg (86%) of an inseparable 1:1 mixture of diastereomeric allylic alcohols (58). A portion (21.6 mg, 0.046 mmol) of this diastereomeric mixture was subjected to deprotection of the silylphenol in the usual manner, yielding mixture of

15  free phenols, separable by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution), to give 7.2 mg (44%) of the less polar 1*S*,3*S* diastereomer (59), along with 6.5 mg (40%) of the more polar 1*R*,3*S* diastereomer (60) as white solids. The 400 MHz $^1$H NMR

20  spectrum and TLC elution properties of each diastereomer 59 and 60 were identical to those previously reported for their respective enantiomeric hydroxy compounds 56 and 57. [Compound 59 is hereinafter also referred to as COMPOUND "B" or 120263]

25  Example 26

(3*S*)-2-Methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethylcyclohexan-1-one (61):

To a flame-dried 50 mL round-bottomed flask containing a 1:1 mixture of silyl-protected phenols 58 (165.0 mg,

30  0.352 mmol) in 12 mL dichloromethane with 2% pyridine at room temperature was added Dess-Martin periodinane reagent (165 mg, 0.386 mmol, 1.1 equiv), and the mixture was stirred for 30 min. The reaction mixture was then transferred to a 125 mL erlynmeyer flask containing 50 mL 1:1

35  saturated aqueous NaHCO$_3$/10% Na$_2$S$_2$O$_3$, and the mixture was stirred for an additional 90 min. The mixture was then
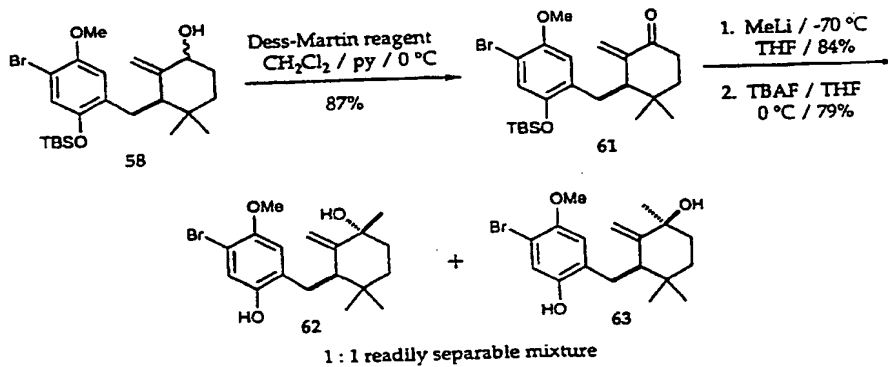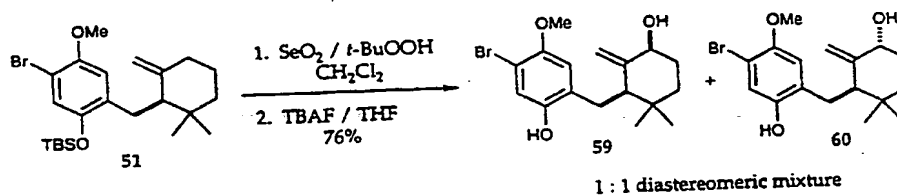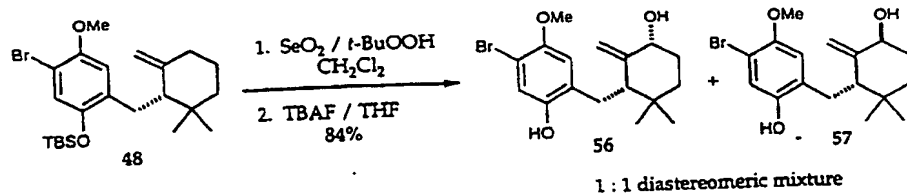
extracted with dichloromethane (2 x 40 mL), and the organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated under diminished pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl

5   acetate, 9:1) afforded 150 mg (91 %) of the desired enone as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.23 (s, 6H, $Si(CH_3)_2$], 1.00 [s, 9H, $SiC(CH_3)_3$], 1.12 and 1.15 (2s, 2 x 3H, geminal-$CH_3$'s), 1.62 (dddd, 1 H, $J$ = 9.9, 6.6, 5.4, 1.3 Hz, 1-$H_{eq}$), 2.01 (dddd, 1H, $J$ = 14.0, 13.8, 8.9, 2.3 Hz, 1

10   -$H_{ax}$), 2.24 and 2.50 (d of ABq, 2H, $J_{AB}$ = 11.9 Hz, $J_A$ = 11.9 Hz, $J_B$ 2.8 Hz, benzylic-$CH_2$), 2.46 and 2.48 (ABq, 2H, $J_{AB}$ = 5.4 Hz, 6-H), 3.07 (dd, 1H, $J$ = 13.3, 3.6 Hz, 3-H), 3.80 (s, 3H, $OCH_3$), 4.46 (d, 1H, $J$ = 1.6 Hz) and 5.54 (d, 1H, $J$ = 1.8 Hz) [methylidene-$CH_2$], 6.41 (s, 1H, 6'-H), 6.93 ppm

15   (s, 1H, 3'- H).

(1R,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-1,4,4-trimethylcyclohexane (62) and (1S,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-1,4,4-trimethylcyclohexane (63).
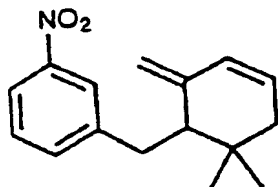
20      To a flame-dried 50 mL round-bottomed flask containing a solution of (3S)-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethylcyclohexan-1-one (61) (150.0 mg, 0.322 mmol) in 15 mL THF at -70°C under nitrogen atmosphere was added methyllithium (0.60 mL of a

25   1.40 M solution in ether, 0.840 mmol, 2.61 equiv), and the mixture was allowed to stir for 5 min before quenching with saturated aqueous $NH_4Cl$. Upon warming to room temperature, the reaction mixture was extracted with ethyl acetate, and the organic phase was washed with brine,

30   dried over $Na_2SO_4$, and concentrated under diminished pressure gave a 3:1 (1R,3S: 1S,3S) mixture of the diastereomeric tertiary hydroxyls. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 28 mg (18%) of the less polar,

35   minor 1S,3S isomer (63), along with 88 mg (57%) of the more polar, major 1R,3S isomer (62), as well as 30.2 mg

51

(20%) recovered starting material. The diastereomeric alcohols were then independently converted to the corresponding free phenols in the usual manner, providing the trans, 1$R$,3$S$ isomer (62) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.84
5  and 1.04 (2s, 2 x 3H, geminal-CH$_3$'s), 1.39 (s, 3H, 5-CH$_3$), 2.43 (br dd, 1H, $J$ _ 11.3, 2.9 Hz, 3-H), 2.72 and 2.85 (d of ABq, 2H, $J_{AB}$ = 16.1 Hz, $J_A$ = 3.1 Hz, $J_B$ = 11.5 Hz, benzylic-CH$_2$) 3.77 (s, 3H, OC$H_3$), 4.57 and 5.16 (2s, 2 x 1H, methylidene-CH$_2$), 6.63 (s, 1H, 6'-H), 6.93 ppm (s, 1H,
10 3'-H); and the cis, 1$S$,3'-H) isomer (63) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.77 and 1.08 (2s, 2 x 3H, geminal-CH$_3$'s), 1.36 (s, 3H, 5-CH$_3$), 2.65 and 2.82 (d of ABq, 2H, $J_{AB}$ = 16.0 Hz, $J_A$ = 3.0 Hz, $J_B$ = 11.8 Hz, benzylic-CH$_2$), 2.97 (br dd, 1H, $J$ = 11.7, 2.5 Hz, 3-H), 3.79 (s, 3H, OC$H_3$), 4.64 and 4.96
15 (2s, 2 x 1H, methylidene-CH$_2$), 6.73 (s, 1H, 6'-H), 6.92 ppm (s, 1H, 3'-H). [Compound 63 is hereinafter also referred to as COMPOUND "J" or 120286, and Compound 62 is hereinafter also referred to as COMPOUND "P" or 120273]
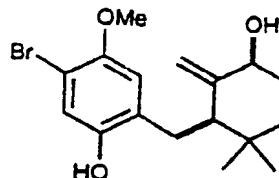
52



1 : 1 diastereomeric mixture



1 : 1 diastereomeric mixture



1 : 1 readily separable mixture

53

Representative derivative compounds include:
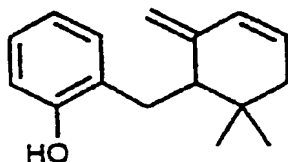
COMPOUND A [120117]
1-Methylidene-6-(3'-
nitrophenyl)methyl-5,5-
dimethylcyclohex-2-ene
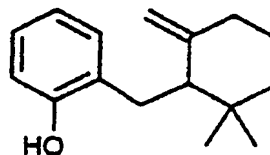
COMPOUND B [120263]
(1S,3S)-1-Hydroxy-2-
methylidene-3-(2'-hydroxy-
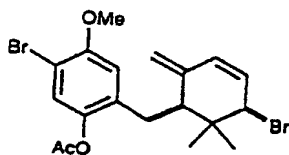4'-bromo-5'-methoxyphenyl)
methyl-4,4-dimethylcyclo-
hexane

COMPOUND C [120363]
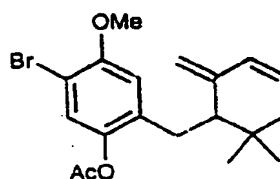1-Methylidene-6-(2'-
hydroxyphenyl)methyl-5,5-
dimethylcyclohex-2-ene

COMPOUND D [120370]
1-Methylidene-2-(2'-
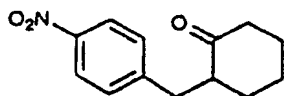hydroxyphenyl)methyl-5,5-
dimethylcyclohexane

COMPOUND E [120261]
(4S,6S)-1-Methylidene-4-
bromo-5-(2'-acetoxy-4'-
bromo-5'methyoxyphenyl)
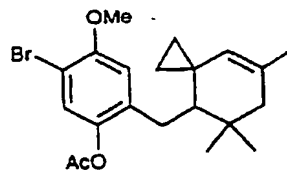methyl-5,5-dimethylcyclo-
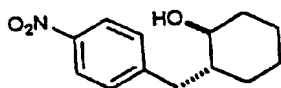hex-2-ene

COMPOUND F [120032]
1-Methylidene-6-(2'-
acetoxy-4'-bromo-5'-
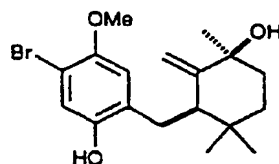methoxyphenyl)methyl-5,5-
dimethyl cyclohex-2-ene

54

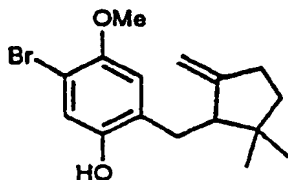COMPOUND G [120138]

2-(4'-Nitrophenyl)methyl-
cyclohexan-1-one

COMPOUND H [120299]

8-(2'-Acetoxy-4'-bromo-5'-
methoxyphenyl)methyl-
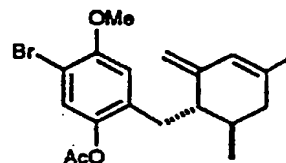5,7,7-trimethylspiro
[2,5]oct-4-ene

COMPOUND I [120154]

trans-2-(4'-Nitrophenyl)
methylcyclohexan-1-ol

COMPOUND J [120286]

(1S,3S)-1-Hydroxy-2-
methylidene-3-(2'-hydroxy-
4'-bromo-5'-methoxyphenyl)
methyl-1,4,4-trimethyl-
cyclohexane

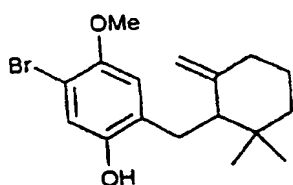COMPOUND K [120192]

1-Methylidene-2-(2'-
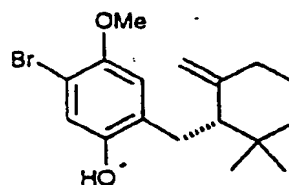hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-3,3-
dimethylcyclopentane

COMPOUND L [120260]

(5R,6S)-1-methylidene-6-
(2'-acetoxy-4'-bromo-5'-
methoxyphenyl)methyl-5-
methylcyclohex-2-ene

55



COMPOUND M [120019]

1-Methylidene-2-(2'-
hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-3,3-
5    dimethylcyclohexane



COMPOUND N [120037]

(2R)-1-methylidene-2-(2'-
hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-3,3-
dimethylcyclohexane



COMPOUND O [120276]

(5R,6S)-1-Methylidene-6-
(2'-acetoxy-4'-bromo-5'-
methoxyphenyl)methyl-3,5-
10    dimethylcyclohex-2-ene



COMPOUND P [120273]

(1R,3S)-1-Hydroxy-2-
methylidene-3-(2'-hydroxy-
4'-bromo-5'-methoxyphenyl)
methyl-1,4,4-trimethyl-
cyclohexane



COMPOUND Q [120136]

*trans*-1-Methyl-2-(2'-
hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-
15    cyclohexan-1-ol



COMPOUND R [120243]

(1R,3R)-1-Hydroxy-2-
methylidene-3-(2'-hydroxy-
4'-bromo-5'-methoxyphenyl)
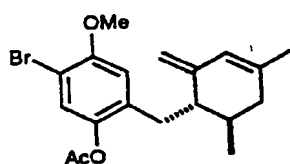methyl-4,4-dimethylcyclo-
hexane

56
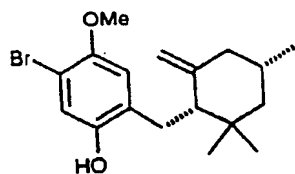


COMPOUND S [120275]
*cis*-1-Methylidene-2-(2'-
hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-
5    3,3,5-trimethyl
cyclohexane
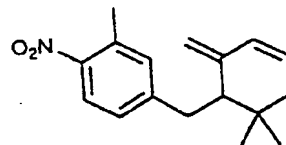


COMPOUND T [120120]
1-Methylidene-6-(3'-
methyl-4'-nitrophenyl)
methyl-5,5-dimethylcyclo-
hex-2-ene



COMPOUND U [120168]
1-Methylidene-6-(3'-
methyl-4'-nitrophenyl)
10   methyl-3,5,5-trimethyl-
cyclohex-2-ene



COMPOUND V [120211]
2-(4'-Nitrophenyl)methyl-
3,3-dimethylcyclohexan-1-
one
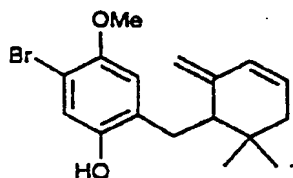


COMPOUND W [120033]
1-Methylidene-6-(2'-
hydroxy-4'-bromo-5'-
15   methoxyphenyl)methyl-5,5-
dimethylcyclohex-2-ene
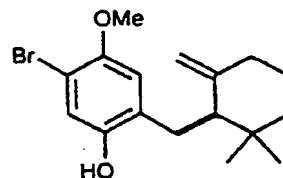


COMPOUND X [120058]
(2*S*)-1-Methylidene-2-(2'-
hydroxy-4'-bromo-5'-
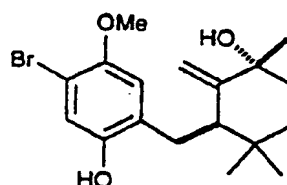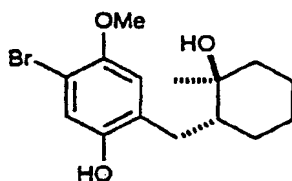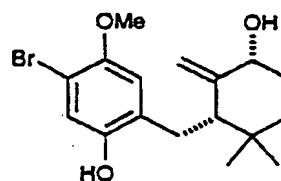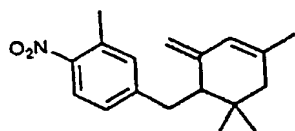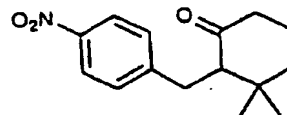methoxyphenyl)methyl-3,3-
dimethylcyclohexane

57
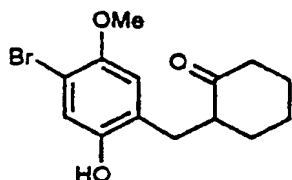


COMPOUND Y [120125]
2-(2'-Hydroxy-4'-bromo-5'-
methoxyphenyl)methylcyclo-
hex-1-one

## Androgen Receptor Activity

Utilizing the "cis-trans" or "co-transfection" assay
described by Evans et al., Science, 240:889-95 (May 13,
1988), the disclosure of which is herein incorporated by
reference, the derivative compounds of Examples 1-26 were
tested and found to have strong, specific antagonist
activity for the intracellular receptor for androgen.
This assay is described in further detail in U.S. Patent
Nos. 4,981,784 and 5,071,773, the disclosures of which are
incorporated herein by reference.  The co-transfection
assay provides a method for identifying functional ligands
(either agonists which mimic, or antagonists which
inhibit, the effect of hormones), and quantifying their
activity for ligand-responsive receptor proteins.  In this
regard, the co-transfection assay mimics an _in vivo_ system
in the laboratory.  Importantly, activity in the co-
transfection assay correlates very well with known _in vivo_
activity, such that the co-transfection assay functions as
a quantitative predicator of a tested compounds _in vivo_
pharmacology. See, e.g., T. Berger et al. 41 J. Steroid
Biochem. Molec. Biol, 773 (1992), the disclosure of which
is herein incorporated by reference.

In the co-transfection assay, a cloned gene for an
intracellular receptor (e.g., androgen receptor) is
introduced by transfection (a procedure to induce cells to

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take up foreign genes) into a background cell substan-
tially devoid of endogenous intracellular receptors. This
introduced gene directs the recipient cells to make the
intracellular receptor protein. A second gene is also
5   introduced (co-transfected) into the same cells in
conjunction with the intracellular receptor gene. This
second gene functions as a reporter for the transcription-
modulating activity of the target intracellular receptor.
Thus, the reporter acts as a surrogate for the products
10  normally expressed by a gene under control of the target
receptor and its natural hormone. A preferred reporter
gene is one which expresses the firefly enzyme luciferase.

The co-transfection assay can detect small molecule
agonists or antagonists of target intracellular receptors.
15  Exposing the cells to an agonist ligand increases reporter
activity in the transfected cells. This activity can be
conveniently measured, e.g., by increasing luciferase
production, which reflects ligand-dependent, intracellular
receptor-mediated increases in reporter transcription. To
20  detect antagonists, the co-transfection assay is carried
out in the presence of a constant concentration of an
agonist (e.g., for androgen receptor, dihydrotestosterone)
known to induce a defined reporter signal. Increasing
concentrations of a test antagonist will decrease the
25  reporter signal (e.g., luciferase production). The co-
transfection assay is therefore useful to detect both
agonists and antagonists of specific intracellular
receptors. It determines not only whether a compound
interacts with a particular intracellular receptor, but
30  whether this interaction mimics (agonizes) or blocks
(antagonizes) the effects of the natural regulatory
molecules on target gene expression, as well as the
specificity and strength of this interaction.

Co-transfected cells are exposed to a medium to which
35  is added the potential ligand (compound) that is being
evaluated. If the candidate compound diffuses into the
cell, binds to the receptor, and the resulting receptor

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complex functions as an agonist, it will subsequently bind to the co-transfected reporter gene and initiate transcription.    Typically, the reporter gene is one that expresses luciferase, which is capable of catalyzing a

5    light-emitting reaction with its substrate luciferin. Thus, after cell lysis and the introduction of luciferin, the amount of light produced relative to the concentration of candidate compound used in the assay provides a measure of the potency and efficacy of the compound tested.

10   Antagonist activity is evaluated by adding the candidate ligand and a known agonist to the co-transfected cells. Suppression of agonist-induced luciferase production by the candidate compound, and hence the amount of light produced, indicates the candidate compound is an

15   antagonist.

The androgen receptor activity of the derivative compounds of Examples 1-26 were demonstrated according to the following illustrative Examples.


Example 27

20   Plasmid pRShAR (produced by cloning the 3400 bp linear fragment of the human androgen receptor (hAR) from vector pGEM3Z (85 P.N.A.S. 7211 (1988)) into the Bam HI site of the pRS vector), which expresses the human androgen receptor was transfected into monkey kidney fibroblast

25   (CV-1) cells along with reporter plasmid MTV-LUC via calcium phosphate precipitation as described in Berger et al. supra.   After six hours, the cells were washed with phosphate-buffered saline (PBS) and incubated at 37°C with 95% $O_2$/5% $CO_2$ for 40 hours prior to harvest.

30   After incubation, whole cell receptor extract was prepared by homogenizing the harvested cells in Tris-HCl buffer, pH=7.4, containing 30% glycerol, 1 mM EDTA, 12 mM monothioglycerol, 1 mM PMSF, and 0.5 M potassium chloride. The homogenate was incubated at 4°C for 60 min with resus-

35   pension every 10 min.   The suspension was centrifuged (105,000 X g, 60 min) and the supernatant was collected

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and flash frozen in liquid nitrogen and stored frozen at -70°C.

Aliquots of the whole cell extract containing transfected androgen receptor were incubated at 4°C for 24 hours with a constant concentration (5 nM) of tritiated dihydrotestosterone (DHT) and increasing concentrations (0 - 2.5 x $10^{-5}$M) of the derivative Compounds A-Y. The concentration of bound tritiated progesterone was determined in each sample by the dextran-coated charcoal adsorption technique, as follows.

To a 500 μl final volume incubation mixture, 400 μl of 7.5% (w/v) dextran-coated charcoal suspension in gelatin phosphate buffer was added. The mixture was vortexed and incubated at 4°C for 10 min and then centrifuged at 3000 rpm for 10 min. The amount of bound tritiated hormone was determined by liquid scintillation spectrophotometry of an aliquot of the supernatant.

The androgen antagonist activity assay results are shown below in Table 1. Efficacy is reported as the % maximal response observed for each compound relative to 2-Hydroxy-flutamide, a compound known to exhibit androgen receptor antagonist activity. Also reported in Table 1 for each compound is its potency or $IC_{50}$ (which is the concentration (nM), required to reduce the maximal response by 50%). Furthermore, the fun androgen antagonist dose response profile of Compounds "A, B, C & D" are shown in FIGS. 2 and 3, relative to the antagonist dose response profile of 2-Hydroxy-flutamide, as shown in FIG. 1. In this regard, the androgen antagonist compounds of the present invention preferably show greater than 60% efficacy and are potent at less than 800 nM, more preferably show greater than 70% efficacy and are potent at less than 500 nM, and most preferably show efficacy of greater than 80% and are potent at less than 300 nM as antagonists to the androgen receptor. Further, the compounds of the present invention selectivity as androgen antagonist is preferably shown by a potency at least three times

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greater, and more preferably at least five times greater than that found on other intracellular receptors (e.g., progesterone receptor, glucocorticoid receptor etc ... ).

5  The specific activity of Compounds A-J was compared relative to their antagonist activity on the human progesterone receptor (PR) utilizing CV-1 cells cotransfected with plasmid pRShPR-B, as altered at the Tau-1 location (e.g., PR-TI) [specifically, HPR-B was excised from the vector pGEM3Z (69 <u>Cell</u> 703 (1992)); the Tau-1 fragment of

10  the glucocorticoid receptor was inserted into hPR-B at the unique HincII site in the N-terminal region; a Bst EII to BST bI fragment spanning the Tau-1 insertion was then used to replace the corresponding region in pRShPR-B]. A comparison of the AR and PR activity of Compounds A-J is

15  shown in Table 2. Efficacy on PR-TI is reported as the % maximal response observed for each compound, and is comparable to that found with RU-486, a compound known to exhibit progesterone receptor antagonist activity. Potency or $IC_{50}$ is as reported for AR-wt transfected CV-1

20  cells. As can be seen, the high specific activity androgen antagonist compounds of the present invention are, in almost all circumstances, at least several times less potent (e.g., require a much higher potency to achieve the same activity), and are often less efficacious as a

25  progesterone antagonist.

Table 1 Inhibitory $IC_{50}$, Efficacy (%) and Potency (nM) of Example Compounds A-Y as Androgen Antagonists.

| Compound | Efficacy (%) | Potency (nM) |
|---|---|---|
| A | 69 | 66 |
| B | 85 | 180 |
| C | 82 | 210 |
| D | 92 | 220 |
| E | 60 | 230 |
| F | 87 | 240 |
| G | 79 | 250 |

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| | | |
|---|---|---|
| H | 89 | 250 |
| I | 85 | 290 |
| J | 85 | 300 |
| K | 91 | 330 |
| L | 88 | 370 |
| M | -- | -- |
| N | 90 | 378 |
| O | 78 | 390 |
| P | 88 | 420 |
| Q | 94 | 460 |
| R | 70 | 500 |
| S | 92 | 500 |
| T | 88 | 545 |
| U | 69 | 565 |
| V | 85 | 590 |
| W | 89 | 610 |
| X | 88 | 723 |
| Y | 67 | 340 |

Table 2

| | CV-1 Cells AR-wt | | CV-1 Cells PR-TI | |
|---|---|---|---|---|
| Compound | Efficacy (%) | Potency (nM) | Efficacy (%) | Potency (nM) |
| A | 69 | 66 | 45 | 3,800 |
| B | 85 | 180 | 98 | 865 |
| C | 82 | 210 | 20 | >10,000 |
| D | 92 | 220 | 73 | 3,500 |
| E | 60 | 230 | 20 | >10,000 |
| F | 87 | 240 | 53 | 820 |
| G | 79 | 250 | 98 | 920 |
| H | 89 | 250 | 26 | 160 |
| I | 85 | 290 | 99 | 360 |
| J | 85 | 300 | 95 | 850 |

The derivative compounds were also individually tested
for cross-reactivity with the other known intracellular
receptor classes. This testing showed the compounds not

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to have significant activity with the glucocorticoid receptor, mineralocorticoid receptor or estrogen receptor.

## Pharmacological and Other Applications

As previously discussed, it has been recognized that
5  the co-transfection assay provides a functional assessment
of the ligand (compound) being tested as either an agonist
or antagonist of the specific genetic process sought to be
affected, and mimics an *in vivo* system in the laboratory.
Compounds which do not react with other intracellular
10  receptors, as determined by the co-transfection assay, can
be expected to result in fewer pharmacological side
effects. Because the co-transfection assay is conducted
in living cells, the evaluation of a compound provides an
early indicator of the potential toxicity of the candidate
15  compound at concentrations where a therapeutic benefit
would be expected.

As will be discernible to those skilled in the art,
the non-steroid androgen receptor antagonist compounds
disclosed can be readily utilized in pharmacological
20  applications where androgen receptor antagonist activity
is desired, and where it is desired to minimize cross
reactivities with other related intracellular receptors.
*In vivo* applications of the invention include administra-
tion of the disclosed compounds to mammalian subjects, and
25  in particular to humans.

The compounds of the present invention are small
molecules which are relatively fat soluble or lipophilic
and enter the cell by passive diffusion across the plasma
membrane. Consequently, these compounds are well suited
30  for administration orally as well as by injection. Upon
administration, these compounds can selectively antagonize
androgen receptors and thereby modulate processes mediated
by these receptors.

The pharmaceutical compositions of this invention are
35  prepared in conventional dosage unit forms by incorporat-
ing an active compound of the invention, or a mixture of

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such compounds, with a nontoxic pharmaceutical carrier according to accepted procedures in a nontoxic amount sufficient to produce the desired pharmacodynamic activity in a mammalian and in particular a human subject.

5    Preferably, the composition contains the active ingredient in an active, but nontoxic, amount selected from about 5 mg to about 500 mg of active ingredient per dosage unit. This quantity depends on the specific biological activity desired and the condition of the patient.

10    The pharmaceutical carrier or vehicle employed may be, for example, a solid or liquid. A variety of pharmaceutical forms can be employed. Thus, when using a solid carrier, the preparation can be plain milled micronized in oil, tableted, placed in a hard gelatin or enteric-coated

15  capsule in micronized powder or pellet form, or in the form of a troche, lozenge, or suppository. When using a liquid carrier, the preparation can be in the form of a liquid, such as an ampule, or as an aqueous or nonaqueous liquid suspension. The following examples provide

20  illustrative pharmacological composition formulations:

Example 28

Hard gelatin capsules are prepared using the following ingredients:

|                                                                    | Quantity (mg/capsule) |
| --- | --- |
| 1-methylidene-6-(3'-nitrophenyl)methyl-5,5-dimethylcyclohex-2-ene (Compound A) | 140 |
| Starch, dried | 100 |
| Magnesium stearate | 10 |
| Total | 250 mg |

The above ingredients are mixed and filled into hard gelatin capsules in 250 mg quantities.

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Example 29

A tablet is prepared using the ingredients below:

|  | Quantity (mg/tablet) |
|---|---|
| Compound A | 140 |
| Cellulose, microcrystalline | 200 |
| Silicon dioxide, fumed | 10 |
| Stearic acid | 10 |
| Total | 360 mg |

10    The components are blended and compressed to form tablets each weighing 665 mg.

Example 30

Tablets, each containing 60 mg of active ingredient, are made as follows:

|  | Quantity (mg/tablet) |
|---|---|
| Compound A | 60 |
| Starch | 45 |
| Cellulose, microcrystalline | 35 |
| Polyvinylpyrrolidone (PVP) (as 10% solution in water) | 4 |
| Sodium carboxymethyl starch (SCMS) | 4.5 |
| Magnesium stearate | 0.5 |
| Talc | 1.0 |
| Total | 150 mg |

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, and then added to the granules

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which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Example 31

Suppositories, each containing 225 mg of active
5   ingredient, may be made as follows:

| | |
|---|---|
| Compound A | 225 mg |
| Saturated fatty acid glycerides | 2,000 mg |
| Total | 2,225 mg |

Consequently, for an understanding of the scope of the
10  present invention, reference is made to the following claims.

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat
15  necessary. The mixture is then poured into a suppository mold of normal 2g capacity and allowed to cool.

Example 32

An intravenous formulation may be prepared as follows:

| | |
|---|---|
| Compound A | 100 mg |
| 20 Isotonic saline | 1,000 mL |
| Glycerol | 100 mL |

The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered
25  intravenously at a rate of 1 mL per minute to a patient.

The compounds of this invention also have utility when labeled as ligands for use in assays to determine the presence of androgen receptor. They are particularly useful due to their ability to selectively activate
30  androgen receptor, and can therefore be used to determine

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the presence of such receptors in the presence of other related receptors.

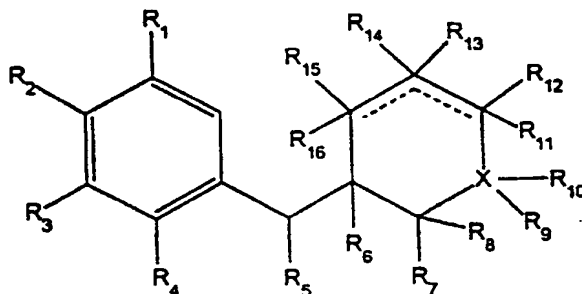Due to the selective specificity of the compounds of this invention for androgen receptor, these compounds can be used to purify samples of androgen receptor *in vitro*. Such purification can be carried out by mixing samples containing androgen receptor with one or more of the derivative compounds disclosed so that the compound (ligand) binds to the receptor, and then separating out the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation, and antibody complexing, among others.

While in accordance with the patent statutes, description of the preferred weight fractions, and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

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We claim:

1.    A compound exhibiting activity as an androgen receptor antagonist having the formulae:



or



5    wherein:

the dotted lines in the structure depict optional double bonds;

X is carbon, oxygen, or nitrogen;

$R_1$ is $R_{17}$, $-OR_{17}$, $-N(R_{17})(R_{17}')$, $-SR_{17}$, fluorine, chlorine,
10    bromine, or $-NO_2$;

$R_{17}$ and $(R_{17}')$, each independently, are hydrogen, saturated or unsaturated $C_1$-$C_6$ alkyl, $C_3$-$C_7$ cycloalkyl, $C_5$-$C_7$ aryl, or $C_7$ aralkyl, said alkyl groups being branched or straight-chain;

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$R_2$ is $-NO_2$, $-N(OH)R_{17}$, fluorine, chlorine, bromine, iodine, $R_{17}$, $-N(R_{17})(R_{17'})$, $-SR_{17}$, $-S(O)-R_{17}$, $-S(O)_2-R_{17}$, $-CH_2OH$, $-C(O)-H$, $-C(O)CH_3$, $-C(O)-OCH_3$, $-C=CH_2$, $-C-CH-C(O)-OCH_3$, or $R_{18}$;

5    $R_{18}$ and $(R_{18'})$, each independently, are hydrogen, saturated or unsaturated $C_1-C_6$ alkyl, $C_3-C_7$ cycloalkyl, $C_5-C_7$ aryl, or $C_7$ aralkyl, said alkyl groups being branched or straight-chain which optionally may contain hydroxyl, aldehyde, ketone, nitrile, or ester groups;

10    $R_3$ is $R_{17}$ or $-OR_{17}$;

$R_4$ is hydrogen, $-OR_{17}$, $-OC(O)R_{17}$, $-OC(O)OR_{17}$, $-OC(O)N(R_{17})(R_{17'})$, $-OS(O)_2R_{17}$, or $-OS(O)-R_{17}$;

$R_5$ is hydrogen or $OR_{17}$;

$R_6$ is $R_{17}$;

15    $R_7$ and $R_8$, each independently, are $R_{18}$, or $R_7$ and $R_8$ together are a carbocyclic 3-8 member ring;

$R_9$ and $R_{10}$, each independently, are chlorine, bromine, or $R_{17}$, or $R_9$ and $R_{10}$ combined are $=O$, except when $X=O$, $R_9$ and $R_{10}$ are not present, and when X is N, then $R_{10}$ is not

20    present, or $R_9$ and $R_{10}$ together are joined in a carbocyclic 3-8 member ring;

$R_{11}$ and $R_{12}$, each independently, are $-OR_{17}$, $R_{18}$, are $=O$, or are $=CH_{2'}$, except when $R_{11}$ is attached to an $sp^2$ carbon atom in the ring, then $R_{12}$ is not present and $R_{11}$ is $R_{18}$,

25    or $R_{11}$ and $R_{13}$ together are joined in a carbocyclic 3-8 member ring or are $-O-$ to form an epoxide;

$R_{13}$ and $R_{14}$, each independently, are $-OR_{17}$ or $R_{18}$, except when $R_{13}$ is attached to an $sp^2$ carbon atom in the ring, then $R_{14}$ is not present and $R_{13}$ is $-OR_{17}$ or $R_{18}$;

30    $R_{15}$ and $R_{16}$, each independently, are $R_{18}$ or $OR_{17}$, or $R_{15}$ and $R_{16}$ together are $-CH_2-O-$ forming an epoxide, or $R_{15}$ and $R_{16}$ combined are $=O$ or $=C(R_{18})(R_{18'})$, except when $R_{15}$ is hydroxyl, then $R_{16}$ is not hydroxyl, and when $R_{15}$ is attached to an $sp^2$ carbon atom in the ring, then $R_{16}$ is not present,

35    and when $R_{15}$ and $R_{16}$ combined are $=O$, then $R_1$, $R_2$, $R_3$, and $R_4$ cannot all be hydrogen nor can $R_3$ be $OCH_3$ when $R_1$, $R_2$, and

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R$_4$ are all hydrogen, or R$_{15}$ and R$_{16}$ together are joined in a carbocyclic 3-8 member ring.

2. A compound according to claim 1, wherein said compound is an optically pure 2R diastereomer.

5      3. A compound according to claim 1, wherein said compound is a optically pure 2S diastereomer.

4. A compound according to claim 1, selected from the group consisting of 1-Methylidene-6-(3'-nitrophenyl) methyl-5,5-dimethylcyclohex-2-ene,    (1S,3S)-1-Hydroxy-2-
10   methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl) methyl-4,4-dimethylcyclohexane,    1-Methylidene-6-(2'-hydroxyphenyl)methyl-5,5-dimethylcyclohex-2-ene,    1-Methylidene-2-(2'-hydroxyphenyl)methyl-5,5-dimethyl-cyclohexane, (4S,6S)-1-Methylidene-4-bromo-5-(2'-acetoxy-
15   4'-bromo-5'-methyoxyphenyl)methyl-5,5-dimethylcyclohex-2-ene,    1-Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxy-phenyl)methyl-5,5-dimethylcyclohex-2-ene,    2-(4'-Nitro-phenyl) methylcyclohexan-1-one, 8-(2'-Acetoxy-4'-bromo-5'-methoxyphenyl)methyl-5,7,7-trimethylspiro[2.5]oct-4-ene,
20   trans-2-(4'-Nitrophenyl)methylcyclohexan-1-ol, (1S,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxy-phenyl)methyl-1,4,4-trimethylcyclohexane, 1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-3,3-dimethyl-cyclopentane,    (5R,6S)-1-Methylidene-6-(2'-acetoxy-4'-
25   bromo-5'-methoxyphenyl)methyl-5-methylcyclohex-2-ene, 1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl) methyl-3,3-dimethylcyclohexane, (2R)-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-3,3-dimethyl-cyclohexane,  (5R,6S)-1-Methylidene-6-(2'-acetoxy-4'-bromo-
30   5'-methoxyphenyl)methyl-3,5-dimethylcyclohex-2-ene, (1R,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-1,4,4-trimethylcyclohexane, trans-1-Methyl-2-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-cyclohexan-1-ol,    (1R,3R)-1-Hydroxy-2-methylidene-3-(2'-

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hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethyl-
cyclohexane, cis-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-3,3,5-trimethylcyclohexane,     1-
Methylidene-6-(3'-methyl-4'-nitrophenyl)methyl-5,5-
5   dimethylcyclohex-2-ene,     1-Methylidene-6-(3'-methyl-4'-
nitrophenyl)methyl-3,5,5-trimethylcyclohex-2-ene,   2-(4'-
Nitrophenyl)methyl-3,3-dimethyl    cyclohexan-1-one,     1-
Methylidene-6-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)
methyl-5,5-dimethylcyclohex-2-ene,   (2S)-1-Methylidene-2-
10  (2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-3,3-dimethyl-
cyclohexane, and 2-(2'-Hydroxy-4'-bromo-5'-methoxyphenyl)
methylcyclohex-1-one.


       5.    A ligand-receptor complex formed by binding of a
compound of claim 1 to an androgen receptor.


15     6.    A ligand-receptor complex formed by binding a
compound of claim 4 to a androgen receptor.


       7.    A pharmacological composition comprising a
pharmaceutically acceptable vehicle and one or more of the
compounds of claim 1.


20     8.    A pharmacological composition comprising a
pharmaceutically acceptable vehicle and one or more of the
compounds of claim 4.


       9.    A method of purifying a enantiomer of a compound
of claim 1, comprising converting said diastereomer to an
25  acetate and separating the diastereomeric acetate.


       10.   The method of claim 9 wherein the separation is
carried out using HPLC.


       11.   A method of antagonizing androgen activity
comprising the _in vivo_ administration of one or more of
30  the compounds of claim 1.

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12. A method for treating a mammalian subject requiring androgen receptor antagonist therapy comprising administering to such subject a pharmaceutically effective amount of a compound of claim 1.

5          13. A method for modulating a process mediated by androgen receptors comprising causing said process to be conducted in the presence of at least one compound as set forth in claim 1.

14. A method for modulating a process mediated by
10   androgen receptors comprising administering to a mammalian subject an amount, effective to moderate said process mediated by said androgen receptors, of a compound of claim 1.

15. A method for determining the presence of one or
15   more androgen receptors comprising combining at least one compound of claim 1 with a sample containing one or more unknown receptors and determining whether said compound binds to any receptor in said sample.

16. A method of purifying androgen receptors compris-
20   ing combining at least one compound of claim 1 with a sample containing androgen receptors, allowing said compound to bind said androgen receptors, and separating out the bound combination of said compound and said androgen receptors.

25       17.          1-Methylidene-6-(3'-nitrophenyl)methyl-5,5-dimethylcyclohex-2-ene,    (1S,3S)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)methyl-4,4-dimethyl-cyclohexane,  1-Methylidene-6-(2'-hydroxyphenyl)methyl-5,5-dimethylcyclohex-2-ene,  1-Methylidene-2-(2'-hydroxyphenyl)
30   methyl-5,5-dimethylcyclohexane,  (4S,6S)-1-Methylidene-4-bromo-5-(2'-acetoxy-4'-bromo-5'-methyoxyphenyl)methyl-5,5-dimethylcyclohex-2-ene,    1-Methylidene-6-(2'-acetoxy-4'-

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bromo-5'-methoxyphenyl)methyl-5,5-dimethylcyclohex-2-ene,
trans-2-(4'-Nitrophenyl)methylcyclohexan-1-ol, (1S,3S)-1-
Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxy-
phenyl)methyl-1,4,4-methylcyclohexane, (5R,6S)-1-
5   Methylidene-6-(2'-acetoxy-4'-bromo-5'-methoxyphenyl)
methyl-3,5-dimethylcyclohex-2-ene, (1R,3S)-1-Hydroxy-2-
methylidene-3-(2'-hydroxy-4'-bromo-5'-methoxyphenyl)
methyl-1,4,4-trimethylcyclohexane, trans-1-Methyl-2-(2'-
hydroxy-4'-bromo-5'-methoxyphenyl) methylcyclohexan-1-ol,
10   (1R,3R)-1-Hydroxy-2-methylidene-3-(2'-hydroxy-4'-bromo-5'-
methoxyphenyl)methyl-4,4-dimethylcyclohexane, 1-
Methylidene-6-(3'-methyl-4'-nitrophenyl)methyl-3,5,5-
trimethylcyclohex-2-ene, 2-(4'-Nitrophenyl)methyl-3,3-
dimethyl cyclohexan-1-one, 1-Methylidene-6-(2'-hydroxy-4'-
15   bromo-5'-methoxyphenyl)methyl-5,5-dimethylcyclohex-2-ene,
(2S)-1-Methylidene-2-(2'-hydroxy-4'-bromo-5'-methoxy-
phenyl)methyl-3,3-dimethylcyclohexane, and 2-(2'-Hydroxy-
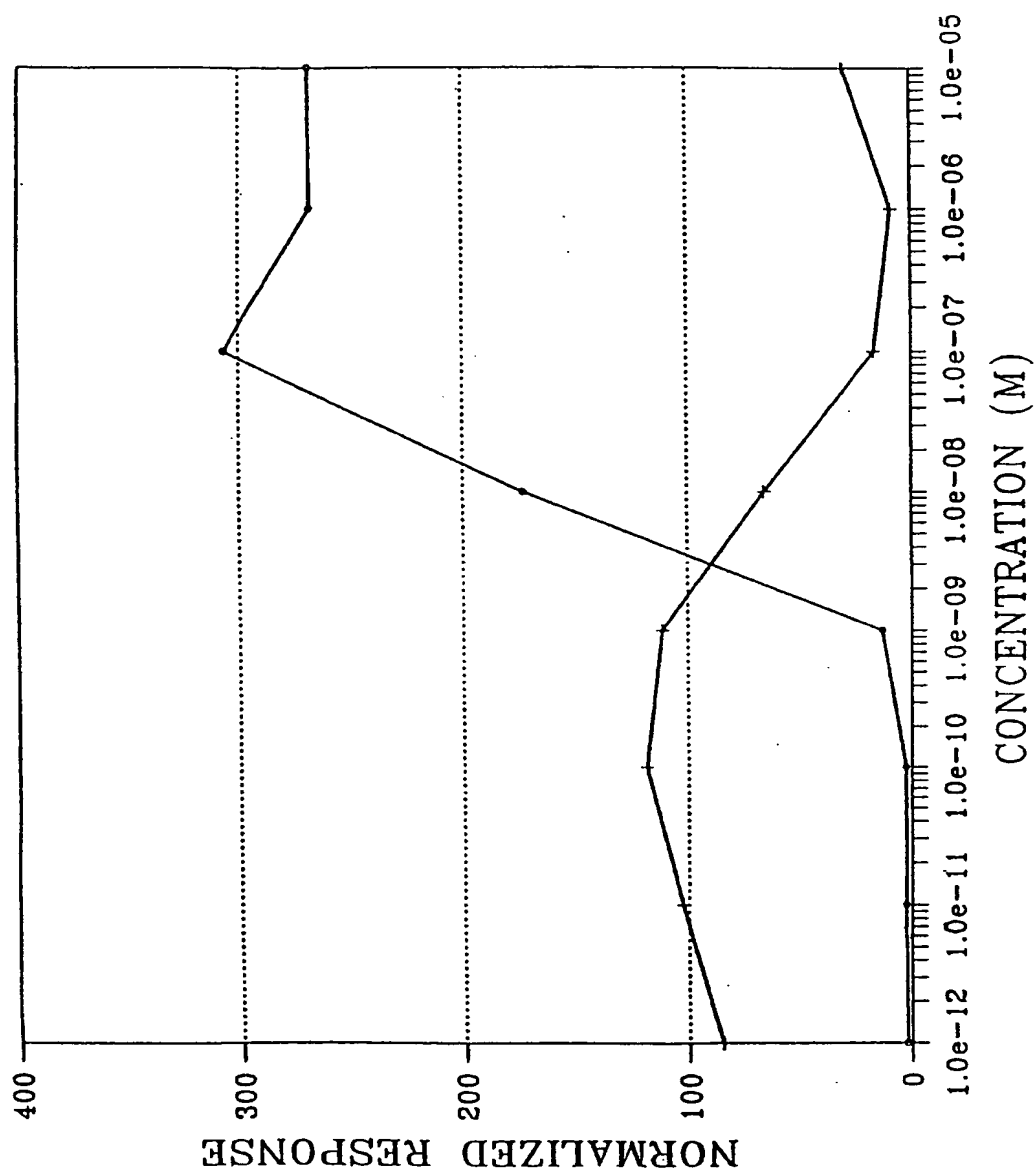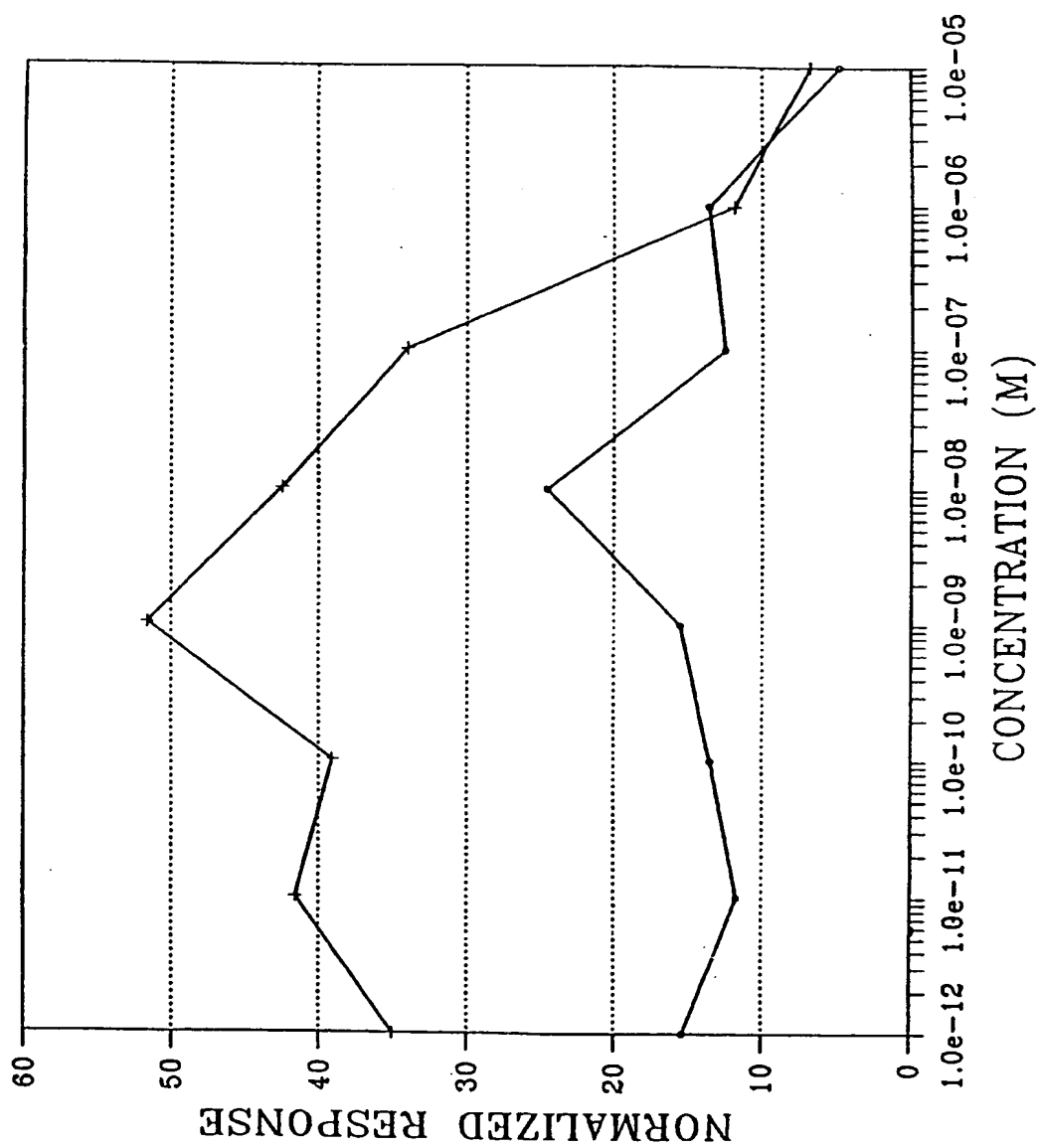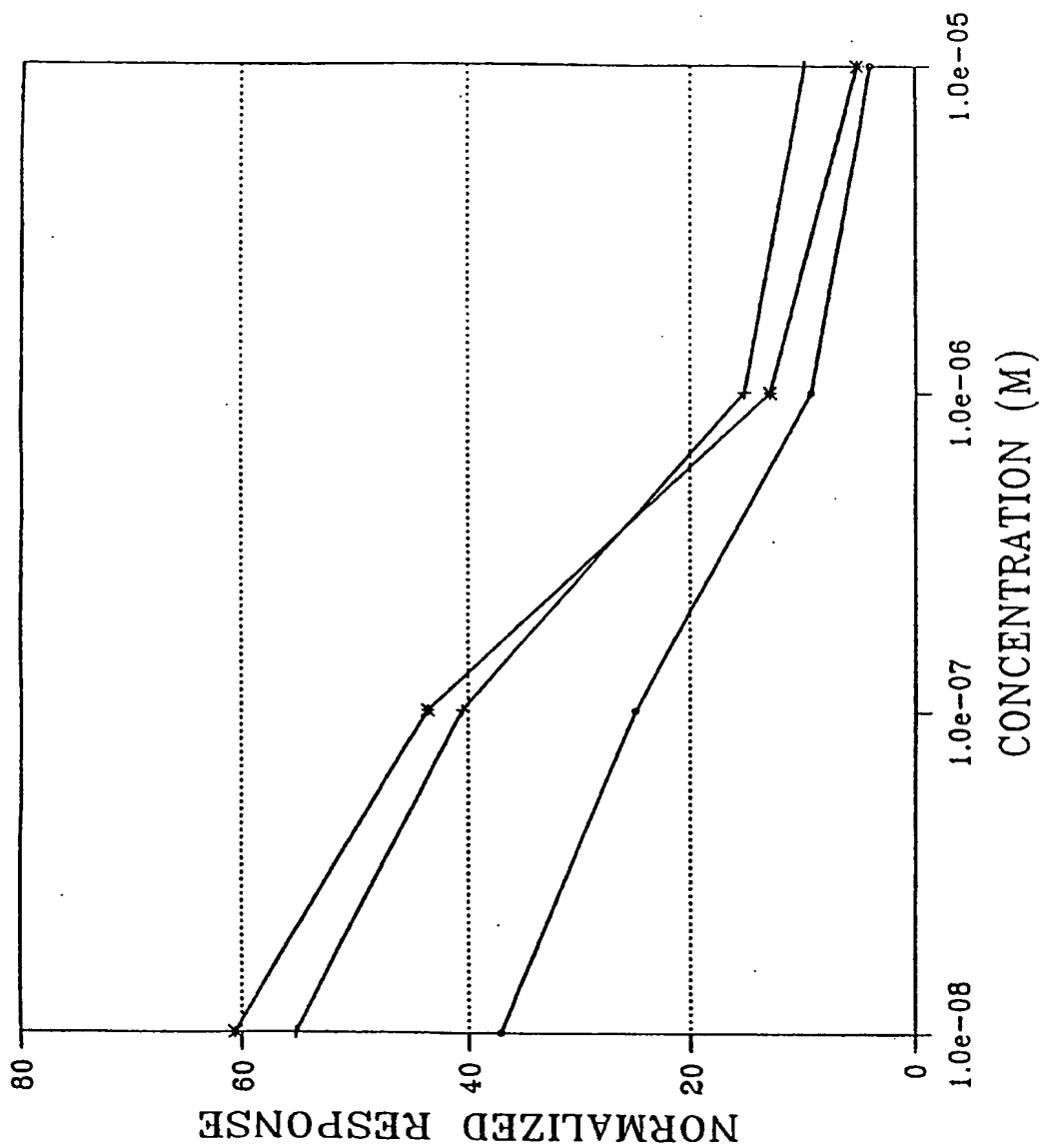4'-bromo-5'-methoxyphenyl)methylcyclohex-1-one.

FIG. 1

FIG. 2

FIG. 3

# INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 6   C07C43/23      C07C69/017     C07C49/517    C07C205/45    C07C205/06
        C07C205/18     C07C39/23      A61K31/085    A61K31/22     A61K31/12
        A61K31/04      A61K31/05

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 6   C07C   A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | JOURNAL OF NATURAL PRODUCTS, vol. 52, no.5, September 1989 – October 1989 COLUMBUS, OHIO, US, pages 1092-1099, M.E. WALL, ET AL.: 'Plant mutagenic agents, 7. Structure and antimutagenic properties of cymobarbatol and 4-isocymobarbatol, new cymopols from green alga (Cymopolia barbata)' see compound 2 | 1 |
| X | AGRICULTURAL AND BIOLOGICAL CHEMISTRY, vol. 54, no.1, January 1990 TOKYO JP, pages 121-123, A. TANAKA, ET AL.: 'Synthesis of (+/-)-cyclocymopol' see compounds 1,2,4 | 1 |

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| [X] | Further documents are listed in the continuation of box C. | | [X] | Patent family members are listed in annex. |
|---|---|---|---|---|

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 6 February 1995 | 1 6. 02. 95 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax ( + 31-70) 340-3016 | Authorized officer<br><br>English, R |

Form PCT/ISA/210 (second sheet) (July 1992)

**page 1 of 5**

## INTERNATIONAL SEARCH REPORT

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|---|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | PHYTOCHEMISTRY, vol. 21, no.3, 1982 OXFORD, GB, pages 2139-2141, O.J. MCCONNELL, ET AL.: 'Diasteroisomers of cyclocymopol monomethyl ether from Cymopolia barbata' see compounds 1a,1b,2a,2b | 1 |
| X | JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no.16, 1976 LETCHWORTH GB, pages 1696-1701, H.-E. HÖGBERG, ET AL.: 'The cymopols, a group of prenylated bromohydroquinones from the green calcareous alga Cymopollia barbata' see compounds 3,4 | 1 |
| X | JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 110, no.10, 11 May 1988 WASHINGTON, DC US, pages 3296-3298, S. AOKI, ET AL.: 'Palladium-catalysed arylation of siloxycyclopropanes with aryl trifliates. Carbon chain elongation via catalytic carbon-carbon bond cleavage' see table II, products in 2nd and 3rd entries | 1 |
| X | JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no.1, January 1990 LETCHWORTH GB, pages 49-51, K. LAUMEN, ET AL.: 'Enzymic preparation of entiomerically pure cyclohexanols: ester synthesis by irreversible acyl transfer' see compound 1,1a | 1-3 |
| X | JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, no.22, 15 November 1991 LETCHWORTH GB, pages 1591-1593, S. PAL, ET AL.: 'A highly regioselective 6-endo-aryl radial cyclisation: sterocontrolled synthesis of trans.octahydroanthracenes' see compound 4 | 1 |

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Inten.    .al Application No

PCT/US 94/11852

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|---|---|---|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | CHEMISTRY LETTERS,<br>no.8, 1991 TOKYO JP,<br>pages 1413-1416,<br>K. NARASAKA, ET AL.: 'Rearrangement of allylic and propargylic alcohols catalysed by the combined use of tetrabutylammonium perrhenate(VII) and p-toluenesulphonic acid'<br>see compound 7<br>--- | 1 |
| X | TETRAHEDRON,<br>vol. 48, no.11, 13 March 1992 OXFORD GB,<br>pages 2059-2068,<br>K. NARASAKA, ET AL.: 'Rearrangement of allylic and propargylic alcohols catalysed by the combined use of tetrabutylammonium perrhenate(VII) and p-toluenesulphonic acid'<br>see compounds 7,7'<br>--- | 1 |
| X | JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS,<br>no.8, 15 April 1992 LETCHWORTH GB,<br>pages 596-568,<br>C. DESTABEL, ET AL.: 'A novel sequence of radical rearrangements involving the 5-exo cyclisation of a 3-(methylenecyclopropyl)-propyl radical'<br>see compounds 6,16<br>--- | 1 |
| X | SYNTHESIS,<br>no.11, November 1992 STUTTGART DE,<br>pages 1073-1075,<br>S. PAL, ET AL.: 'A facile synthetic route to 1,1-disubstituted 2,3-dihydro-1H-benz[f]indene-4,9-diones'<br>see compound 1b<br>--- | 1 |
| X | TETRAHEDRON,<br>vol. 42, no.20, 1986 OXFORD GB,<br>pages 5637-5640,<br>S. ANTUS, ET AL.: 'Synthesis of grisan'<br>see compounds 7,8<br>--- | 1 |
| X | JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,<br>vol. 115, no.10, 19 May 1993 WASHINGTON, DC US,<br>pages 3909-3917,<br>J.-L. REYMOND, ET AL.: 'Antibody-catalysed hydroylsis of enol ethers'<br>see page 3916, right column, line 23 - line 36<br>--- | 1 |

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# INTERNATIONAL SEARCH REPORT

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 65, no.9, November 1992 TOKYO JP, pages 2421-2426, H. NAGANO, ET AL.: 'Radical-based synthesis of terpenoids. Steroselectivity in the trapping of radicals from the cyclisation of 3-(1-ethoxy-2-haloethoxy)-cyclohexenes' see compounds 21,21' --- | 1 |
| X | EXPERIENTIA, vol. 34, no.9, 15 September 1978 BASEL CH, pages 1124-1125, J.P. YARDLEY, ET AL.: 'A potent benzylamine analgesic: (-)-cis-2-(alpha-dimethylamino-m-hydroxy-benzyl)cyclohexanol' see compound 6 --- | 1,3 |
| X | BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, no.4, 1969 PARIS FR, pages 1362-1367, M. MOREAU, ET AL.: 'Hydroxy-4a hexahydro-1,2,3,44a,9a xanthene. III. Étude de la tautomérie anneau-cha*ne' see compounds 6-10,12a,12b,13,14a,14b --- | 1 |
| X | JOURNAL OF THE INDIAN CHEMICAL SOCIETY, vol. 42, no.6, 1969 CALCUTTA, IN, pages 415-423, K. DAS GUPTA 'Hydrofluorene derivatives. I. Synthesis of 1,6- and 1,7-dimethyl- and 7-hydroxy-1-methylfluorenes' see compound XV --- | 1 |
| X | US,A,5 134 155 (P.J. CONNOLLY, ET AL.) 28 July 1992 see column 17, table 1, compounds 86,88-95 --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 66, no. 21, 22 May 1967 Columbus, Ohio, US; abstract no. 94773s, A.I. CHIRKO, ET AL.: 'Autooxidation of benzyl cycloparaffins' page 8859; see abstract, in particular compounds III,IV and 'phenyl(2-hydroxycyclohexyl)-methane' & ZHURNAL ORGANISCHESKOI KHIMII, vol. 3, no.1, 1967 pages 28-33, --- | 1 |

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3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT .

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| --- | --- | --- |
| X | PROCEEDINGS OF THE INDIAN ACADEMY OF SCIENCES, SECTION A, vol. 86A, no.3, 1977 BANGALORE, IN, pages 317-325, J. CHARRAVARTY, ET AL.: 'Condensed cyclic and bridged-ring systems. VII. Acid-catalysed cyclisation of methyl-substituted benzylcyclohexanols. Factors influencing the nature of cyclisation products' see compounds 6, 11, 16 --- | 1 |
| P,X | WO,A,93 21145 (LIGAND PHARMACEUTICALS) 28 October 1993 see page 8 - page 10; claims 1-9; examples 7-22 ------ | 1-4,17 |

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**Box I   Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:      1-17
   .because they relate to subject matter not required to be searched by this Authority, namely:

   ## SEE ATTACHED SHEET

2. [ ] Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**              [ ] The additional search fees were accompanied by the applicant's protest.

                                   [ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

**FURTHER INFORMATION CONTINUED FROM    PCT/ISA/210**

CLAIMS SEARCHED INCOMPLETELY : 1-17

CLAIMS 1-17 ENCOMPASS SUCH A LARGE NUMBER AND VARIETY OF COMPOUNDS THAT A
COMPLETE SEARCH IS NOT POSSIBLE ON ECONOMIC GROUNDS (GUIDELINES FOR EXAMI-
IN THE EPO, PART B, CHAPTER III, 3.7). THUS THE SEARCH WAS DIRECTED TOWARDS
(BUT NOT LIMITED TO) COMPOUNDS HAVING VARIABLES AS REPRESENTED IN THE
EXAMPLES AND IN CLAIMS 4, 17. FURTHERMORE, SINCE AN ABILITY TO ANTAGONISE
ANDROGEN RECEPTORS AS THIS CANNOT BE DETERMINIED FROM PRIOR ART DOCUMENTS
UNLESS IT HAS BEEN SPECIFICALLY MENTIONED, THE SEARCH FOR CLAIMS 1-4 WAS
NOT NECESSARILY LIMITED TO COMPOUNDS WITH THIS ACTIVITY.
REMARK : ALTHOUGH CLAIMS 11-14 ARE DIRECTED TO A METHOD OF TREATMENT OF THE
HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED
EFFECTS OF THE COMPOUND.

Inten    1al Application No

**PCT/US 94/11852**

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| US-A-5134155 | 28-07-92 | AU-A- | 2058992 | 11-02-93 |
| | | EP-A- | 0529854 | 03-03-93 |
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| | | US-A- | 5315012 | 24-05-94 |
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| | | AU-B- | 5664194 | 08-11-94 |
| | | CA-A- | 2133325 | 28-10-93 |
| | | EP-A- | 0637296 | 08-02-95 |
| | | WO-A- | 9424080 | 27-10-94 |